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MECHANISMS OF CARCINOGENESIS

Macromolecular Alteration and Repair

SERIES CK11 No. 82/01 JANUARY, 1982

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

BIOLOGICAL ASPECTS OF DNA ALTERATION AND REPAIR IN RELATION TO CARCINOGENICITY

1. MODULATION OF IN VITRO TRANSFORMATION AND THE EARLY AND LATE MODES OF DNA REPLICATION OF UV-IRRADIATED SYRIAN HAMSTER CELLS BY CAFFEINE.

Doniger J, DiPaolo JA
Lab. Biology, NCI, Bethesda, MD, 20205
Radiat Res; 87(3):565-575 1981

The relationship between the effect of caffeine (CF) on post-UV DNA synthesis and its effects on transformation were studied in fresh tertiary Syrian hamster embryo cells (HEC). When HEC treated with 3 joules/square meter radiation were incubated in the presence of CF (0.25 milliM) for 48 hr, the UV-induced transformation frequency was 2-5-fold higher than that obtained with UV irradiation alone. The degree of enhancement by CF was dependent on the interval between UV irradiation and CF addition. Thirty min after HEC were UV-irradiated, the pulse-labeled DNA nascent strands were much smaller than the nonirradiated controls. The addition of CF immediately after UV irradiation had little or no effect on the size of nascent strands during the first 1.5 hr. However, the recovery of size of the nascent strands observed 5-7 hr post-UV was inhibited by CF. Thus, CF inhibited the occurrence of the late mode of replication. During the early mode of replication CF inhibited the rate of elongation of nascent daughter strands in UV-irradiated HEC. CF inhibited the enhancement of chain elongation associated with pretreatment by low UV dose, but had no effect on the size distribution of nascent strands in cells that were pulse-labeled at 0.5 hr post-UV but not chased. CF was also able to convert the late-mode replication back to the early mode. (19 Refs)

2. DNA STRAND BREAKS AND REPAIR SYNTHESIS IN YOSHIDA SARCOMA: CELLS WITH DIFFERENTIAL SENSITIVITIES TO BIFUNCTIONAL ALKYLATING AGENTS AND UV LIGHT.

Carr FJ, Fox BW
(c/o Fox) Paterson Lab., Christie Hosp., Manchester M20 9BX, England
Mutat Res; 83(2):233-249 1981

Analysis of the incidence of DNA strand breaks induced in Yoshida sarcoma cells sensitive (YS) to and resistant (YR) to methylene dimethanesulfonate (MDMS) by MDMS (a bifunctional alkylating agent), UV radiation, and methyl methanesulfonate (MMS; a monofunctional alkylating agent) was carried out using an alkaline DNA unwinding-hydroxylapatite technique to detect the breaks. Treatment with up to 200 ug/ml MDMS in either exponential or plateau phase of growth produced almost identical numbers of breaks in both YS and YR cells in both growth phases when breaks were measured immediately after MDMS treatment; but when the cells were post-incubated for up to 12 hr after MDMS treatment, the incidence of breaks was lower in YR than in YS cells throughout the period and for both growth phases. Treatment of these cells (prior to, during, or after MDMS treatment) with either 1-beta-D-arabinofuranosylcytosine or hydroxyurea, which inhibited gap closure, revealed equal incidence of breaks in YS and YR cells. When plateau-phase YS and YR cells were treated with UV light (5 or 20 joules/square meter), the incidence of strand breaks was similar in both lines up to 2 hr after treatment, when the incidence in YR cells declined to below that in YS cells. Treatment of YS and YR cells with MMS (50 mg/ml for 1 hr) produced no significant difference in the incidence of strand breaks at any time up to 12 hr after treatment; the decay in the number of breaks was much slower than that observed after MDMS treatment. When the rate of repair synthesis induced by MDMS amd MMS in YS and YR cells was assayed by the BND-cellulose method, YR cells showed greater repair activity in the 12-hr period after drug treatment, which agrees with the other results obtained here. YR and YS cells appear to have equal capacities for making repair incisions in DNA, but YR cells can close the incision-repair gaps more efficiently than can YS cells. (35 Refs)

3. LIGHT-INDUCED CHROMATID DAMAGE IN HUMAN SKIN FIBROBLASTS IN CULTURE IN RELATION TO THEIR NEOPLASTIC POTENTIAL.

Parshad R, Gantt R, Sanford KK, Jones GM, Camalier RF
Dept. Pathology, Coll. Medicine, Howard Univ., Washington, DC, 20059
Int J Cancer; 28(3):335-340 1981

Skin fibroblasts from ataxia telangiectasia and xeroderma pigmentosum (XP) donors and from the XP sib (possible heterozygote), all genetically predisposed to a high risk of cancer, show an increased susceptibility to light-induced chromatid breaks after culture in vitro. Light-induced chromatid breaks were shown previously to result from generation of hydrogen peroxide (H_2O_2) during light exposure. The level of susceptibility attained is significantly higher than that observed in 13 lines of fibroblasts from normal skin of donors ranging in age from 3 days to 92 yr or from fetal skin tested at various population doubling levels. Two lines of normal skin fibroblasts transformed by chemical carcinogens to neoplastic cells also show a significant increase in susceptibility as compared with their untransformed controls. These data indicate for human cells, as reported earlier for mouse cells, an association between enhanced susceptibility to light-induced chromatid damage and neoplastic potential; this association is further supported by the high susceptibility of cells derived from a human adenocarcinoma. Two observations are consistent with the concept that the increased susceptibility does not result from greater initial damage to the DNA of the neoplastic cells. First, activities of the ubiquitous H_2O_2 scavenging enzyme, glutathione peroxidase, are similar in the paired normal and neoplastic cell populations. Second, cells of the paired lines are equally sensitive to DNA breakage by exogenous H_2O_2. The enhanced susceptibility associated with neoplastic potential may result from an impaired capacity to repair DNA rather than a greater initial sensitivity of the neoplastic cells to the damaging agent. (Author abstract) (35 Refs)

4. SENSITIVITY OF EXCISION REPAIR IN NORMAL HUMAN, XERODERMA PIGMENTOSUM VARIANT AND COCKAYNE'S SYNDROME FIBROBLASTS TO INHIBITION BY CYTOSINE ARABINOSIDE.

Cleaver JE
Lab. Radiobiology, Univ. California, San Francisco, San Francisco, CA, 94143
J Cell Physiol; 108(2):163-173 1981

The effects of cell type, cell cycle stage, deoxycytidine pool sizes, concentrat ion of 1-beta-D-arabinofuranosylcytosine (ara-C), and the structure of the aborted repair patch on inhibition of excision repair by ara-C were studied. Primary human cells were obtained by skin biopsy from normal, xeroderma pigmentosum (XP) variant, and Cockayne's syndrome humans. Paren-

tal DNA was labeled by growth in 14C-thymidine for at least two to three generations. S-phase cells were labeled with 3H-thymidine. Cultures were then exposed to UV, 13 joules/square meter, with a 5 hr incubation time. With or without hydroxyurea (HU), ara-C inhibited repair of UV damage and resulted in the accumulation of single-strand breaks in DNA during the G1 and G2 phases. The S-phase was resistant to ara-C inhibition, apparently because of either the presence of a pool of deoxycytidine nucleotides during S-phase or the changing roles of different DNA polymerases. Normal and Cockayne's syndrome cells showed similar numbers of breaks, with XP variant cells slightly higher. The number of breaks increased with increasing concentrations of ara-C. HU, when added to ara-C, extended the inhibition into the S-phase. The results suggest that repair proceeds so that both the damaged segment and the repair patch remain attached to the larger DNA strand. Digestion of DNA with exonuclease III indicated that the size of the patch is about 100 nucleotides. (48 Refs)

5. DNA REPAIR ENZYME DEFICIENCY AND IN VITRO COMPLEMENTATION OF THE ENZYME ACTIVITY IN CELL-FREE EXTRACTS FROM ATAXIA TELANGIECTASIA FIBROBLASTS.

Inoue T, Yokoiyama A, Kada T

Dept. Induced Mutation, Natl. Inst. Genetics, Mishima, Shizuoka-ken 411, Japan

Biochim Biophys Acta; 655(1):49-53 1981

Three ataxia telangiectasia homozygotes, one heterozygote and normal fibroblast strains were compared as to the capacity of their cellular extracts to enhance the priming activity of gamma-irradiated colicin E1 DNA for purified DNA polymerase (EC 2.7.7.7) of Escherichia coli. It was found that homozygotes had substantially lower activity than normal strains, while no difference was detected between the heterozygote and normal strains. In vitro complementation of the activity occurred between extracts of certain strains of homozygotes, allocating them to two complementation groups. (Author abstract) (11 Refs)

6. FLUORESCENT-LIGHT-INDUCED LETHALITY AND DNA REPAIR IN NORMAL AND XERODERMA PIGMENTOSUM FIBROBLASTS.

Ritter MA, Williams JR

Dept. Radiation Therapy, Hosp. Univ. Pennsylvania, 3400 Spruce St., Box 522, Philadelphia, PA, 19104

Biochim Biophys Acta; 655(1):18-25 1981

Cell survival and induction of endonuclease-sensitive sites in DNA were measured in human fibroblast cells exposed to fluorescent light or germicidal UV light. Cells from a xeroderma pigmentosum patient were hypersensitive to cell killing by fluorescent light, although less so than for g ermicidal UV light. Xeroderma pigmentosum cells were deficient in the removal of fluorescent light-induced endonuclease sites that are probably pyrimidine dimers, and both the xeroderma pigmentosum and normal cells removed these sites with kinetics indistinguishable from those for UV light-induced sites. A comparison of fluorescent with UV light data demonstrates that there are markedly fewer pyrimidine dimers per lethal event for fluorescent than for UV light, suggesting a major role for non-dimer damage in fluorescent light lethality. (Author abstract) (40 Refs)

7. A NEW HUMAN PHOTOSENSITIVE SUBJECT WITH A DEFECT IN THE RECOVERY OF DNA SYNTHESIS AFTER ULTRAVIOLET-LIGHT IRRADIATION.

Fujiwara Y, Ichihashi M, Kano Y, Goto K, Shimizu K

Dept. Radiation Biophysics, Kobe Univ. Sch. Medicine, Kusunoki-cho 7-12, Chuo-ku, Kobe 650, Japan

J Invest Dermatol; 77(3):256-263 1981

A sun-sensitive, 8-yr-old male patient (termed UV(8)1KO) with only acute recurrent sunburns and without any other physical or neuromental retardations was studied. The patient's skin exhibited lowered minimal erythema doses between 280 and 300 nm monochromatic wavelengths without delayed peaking of erythema. UV(8)1KO skin fibroblasts in culture were 5-fold more sensitive to 254 nm UV killing than normal cells, though the response of obligatory heterozygotes was normal. UV(8)1KO cells showed defective recovery of DNA synthesis after 254 nm UV irradiation with 1 and 5 J/m2, at which dose the recovery occurred in normal cells. The base line level of sister-chromatid exchanges (SCEs) was higher in UV(8)1KO cells (10-12 SCEs/cell) than in normal cells (5 SCEs/cell), although the induction rate of SCEs by 254 nm UV in UV(8)1KO cells was the same as in normal cells. Clinical, cellular and molecular characteristics and comparison to those in the other photodermatoses can make a clear distinction of UV(8)1KO from the others. Thus, the UV(8)1KO disorder is put forward as a new photodermatosis with a defect in the recovery of post-UV DNA synthesis. (Author abstract) (38 Refs)

BIOLOGICAL ASPECTS OF DNA ALTERATION AND REPAIR IN RELATION TO MUTAGENICITY

8. CARCINOGEN-DNA ADDUCTS IN MUTAGENESIS ASSAYS.

Bigger CA, Dipple A, Tomaszewski JE, Lake RS

Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701

Science; 213(4514):1411-1412 1981

Comparative studies of carcinogen metabolism in different systems to examine the assumption that the subcellular Aroclor-induced rat liver metabolizing system, recommended for general mutagenesis screening, effectively duplicated the activation of carcinogens in target tissue in vivo are described. In a series of studies, it was demonstrated that DNA-reactive metabolites of 7,12-dimethylbenz(a)anthracene generated by Aroclor-induced rat liver microsomes or S9 fraction differ substantially from th ose generated in intact cellular systems in vitro and a target tissue, mouse skin, in vivo. Studies with aflatoxin B1 and benzo(a)pyrene show no DNA adduct data for the Arochlor-induced rat liver system. It was suggested that the specific DNA adducts responsible for carcinogenesis are not known with certainty for any carcinogen, but that there is evidence to show that specific DNA reactive metabolites play a central role in carcinogenesis. Because of the wide application of these liver homogenates as models of in vivo activation in in vitro systems for the detection of potential carcinogens whose structure, pathways of metabolism, and mechanism of action are unknown, it was suggested that the accurate reproduction of in vivo activation cannot be assumed. (9 Refs)

9. SISTER CHROMATID EXCHANGE, DNA REPAIR, AND SINGLE-GENE MUTATION.

Carrano AV, Thompson LH

Lawrence Livermore Natl. Lab., Livermore, CA

Proceedings of the ICN-UCLA Symposia on Mechanisms in Chemical Carcinogenesis, held in Keystone, CO, February 22, 1981. Available from National Technical Information Service, Springfield, VA, as UCRL-85849:, 22 pp., 1981.

Sister chromatid exchange (SCE) has been studied in cultured mammalian cells with regard to the nature of the inducing lesion, mutation induction, and factors that modify the observed frequency following mutagen exposure. SCEs can be induced by a wide spectrum of DNA lesions and, for nine agents examined, the frequency of induced SCE is linearly related to induced single-gene mutation. Further, a deficiency in DNA repair may alter the expression of both SCE and mutation in a quantitatively similar manner. The frequency of SCE induced by mitomycin-C is suppressed in heterochromatin relative to euchromatin and, in non-dividing lymphocytes, the lesions leading to the formation of SCEs may persist for several mo. (Author abstract)

10. ANTIMUTAGENIC ACTIVITY OF CERTAIN DRUGS.

Ostrovskaia AA, Lil'in ET, Glazyrin VF

Lab. Genetical Control of Drug Metabolism, Res. Inst. Biological Tesing of Chemical Compounds, Kupavna, Moscow Oblast', USSR

Farmakol Toksikol; 44(4):467-470 1981

The antimutagenic activity of 11 drugs was studied in cultures of human embryonal fibroblasts (HEF) and xeroderma pigmentosum (XP) cells. Caffeine, hexamidine, LM8 and vitamin E stimulated proliferation of both HEF and XP cells. Ionol stimulated proliferation of HEF but was ineffective in a culture of XP cells. Mutagen dioxidine caused marked inhibition of proliferation of HEF but did not affect proliferation of XP cells. (5 Refs) (In RUS)

11. MUTAGENICITIES OF CARBADOX AND OLAQUINDOX - GROWTH PROMOTERS FOR PIGS.

Yoshimura H, Nakamura M, Koeda T, Yoshikawa K

Second Assay Div., Natl. Veterinary Assay Lab., 1-15-1 Tokura, Kokubunji-shi, Tokyo 185, Japan

Mutat Res; 90(1):49-55 1981

Both carbadox and olaquindox were positive in the Bacillus subtilis rec and in the Salmonella typhimurium uvr repair tests. In the reverse mutation test with S typhimurium TA100 and TA 98, a linear dose-response relationship was observed for both compounds between 0 and 15 ug/plate. Carbadox was more mutagenic than olaquindox and their activities were marked with strain TA100 (respectively, 315.4 vs 46.3 revertants/ug). In the absence of microsomal supernatant (S9), carbadox was approx 6x more mutagenic than olaquindox; in TA100 with S9, the number of revertant colonies decreased to 146.8/ug with carbadox but only to 38.3/ug with olaquindox. S9 incubation inactivated carbadox almost totally after 10 min, whereas olaquindox retained its activity after 20 min. Carbadox required 20 min to be inactivated by a bacterial cytosol mixture; olaquindox was hardly inactivated after 60 min. Carbadox and olaquindox appear to induce frameshift and base-pair substitution mutations as a result of error in the DNA repair process. Significance of the findings is discussed with respect to use of these compounds as growth promoters in pigs. (18 Refs)

12. BACTERIAL MUTAGENICITY AND TOXICITY OF CYCLOALIPHATIC EPOXIDES.

Frantz SW, Sinsheimer JE

(c/o Sinsheimer) Coll. Pharmacy, Univ. Michigan, Ann Arbor, MI, 48109

Mutat Res; 90(1):67-78 1981

The Ames mutagenicity test with Salmonella was used to investigate mutagenicity of 12 cycloaliphatic epoxides without the addition of liver homogenate fractions. Eight compounds exhibited base-pair substitution mutagenic activity. Mutagenicity decreased with expanding ring size, while inhibition of bacterial growth increased with increasing ring size. Epoxide toxicity at the doses required for mutagenicity prevented establishment of meaningful dose-response relationships. Petri dish sealing bands were used to prevent loss of volatile compounds during 48 hr incubation. Mutagenicity was greater in TA1535 than in TA100; toxicity was more pronounced in TA100. Toxicity was not reduced by the use of less permeable strains (TA92, TA1950, and TA2410). Cyclooctane oxide testing with TA1975 (repair-proficient) and TA1535 (repair-deficient) demonstrated that the bacteria were not being killed by damage to DNA, since toxicity was not reduced in TA1975. The results confirm that cis-1,2-disubstituted oxiranes are mutagenic. (26 Refs)

13. A COMPARISON OF AFLATOXIN B1-INDUCED CYTOTOXICITY, MUTAGENICITY AND PROPHAGE INDUCTION IN SALMONELLA TYPHIMURIUM MUTAGEN TESTER STRAINS TA1535, TA1538, TA98 AND TA100.

Wheeler L, Halula M, Demeo M

Dept. Pharmacology and Dental Res. Inst., Univ. California, Los Angeles, CA, 90024

Mutat Res; 83(1):39-48 1981

Aflatoxin B1 (AFB1) was studied for its ability to induce mutagenesis, prophage induction and cytotoxicity in Salmonella typhimurium tester strains TA1535, TA1538, TA98, and TA100. The frame-shifter tester strains TA1538 and TA98 were susceptible to the lethal effects of AFB1 at all doses tested (up to 1,000 nanog) compared to the base-pair tester strains TA1535 and TA100. The differences were statistically significant at 0.1 and 1 ug. Survival in TA98 was not enhanced by the plasmid pKM101 compared to TA1538, but it did enhance survival of TA100 compared to TA1535. SL1027 (a dihydrostreptomycin-resistant indicator organism), and nalidixic acid resistant strains of Q1, Q1 (Fels 1) and Q1 (Fels 2) were constructed for use as phage indicator strains in the Salmonella inductest. Induction of both prophages, Fels 1 and Fels 2, was observed on the appropriate Q1 lysogen after treatment of TA1535 and TA100 with AFB1 (100 nanog or 1 ug) with S9 mix and cofactors. With TA1538 and TA98, prophage, only one phage was observed, Fels 2. These data demonstrate that prophage induction detects DNA damage induced by liver-activated AFB1 in TA1535 and TA1538 that is non-mutagenic in these histidine auxotrophs. Prophage induction may be a useful tandem assay with other standard microbial tests. (27 Refs)

14. FRAMESHIFT MUTATIONS: RELATIVE ROLES OF SIMPLE INTERCALATION AND OF ADDUCT FORMATION.

McCoy EC, Rosenkranz EJ, Petrullo LA, Rosenkranz HS
Center for Environmental Health Sciences, Sch. Medicine, Case Western Reserve Univ., Cleveland, OH, 44106
Mutat Res; 90(1):21-30 1981

The mutagenic properties of 9-aminoacridine, its derivative quinacrine, and the nitro-containing derivative Entozon were examined in Salmonella typhimurium and Escherichia coli WP2uvrA assays. Both 9-aminoacridine and quinacrine induced frameshift mutations in strain TA1537 only (with, respectively, 1.7 and 3.0 revertants/nanomole (r/nm)), confirming the finding that simple intercalators mutate this strain alone. Entozon primarily affected strains TA98 (338 r/nm) and TA1538 (288 r/nm), indicators for frameshift mutations resulting from adduct formation; mutagenicity was greatly decreased when Entozon was tested in strain TA1978 (23 r/nm), the uvrB+ analog of TA1538 which does not respond maximally to the mutagenic action of adduct-forming chemicals as a result of its intact uvrB system. Entozon displayed no base-substitution activity for Salmonella, although it exhibited some activity when tested in E coli WP2uvrA (2.4 r/nm). When a cell is exposed to a molecule inducing frameshift mutations by intercalation and adduct formation, the formation of adducts apparently exerts a much stronger influence on total mutagenic expression. (47 Refs)

15. NITRATED FLUORENE DERIVATIVES ARE POTENT FRAMESHIFT MUTAGENS.

McCoy EC, Rosenkranz EJ, Rosenkranz HS, Mermelstein R
Center for Environmental Health Sciences, Sch. Medicine, Case Western Reserve Un iv., Cleveland, OH, 44106
Mutat Res; 90(1):11-20 1981

The structure-activity relationship of polynitrated polycyclic aromatic hydrocarbons (PAH) which might be present in the environment as a result of incomplete combustion and subsequent nitration by oxides of nitrogen was investigated. The biological activity of 2-nitrofluorene, 2,7-dinitrofluorene, 2,7-diaminofluorene, (2,4,7-trinitro-9-fluorenylidene) malononitrile, 2,4,5,7-tetranitro-9-fluorenone, 2,7-dinitro-9-fluorenone, and 2,4,7-trinitro-9-fluorenone was studied. Significant mutagenic activity was observed for all the compounds in Salmonella typhimurium strains TA1538, TA98, and TA1537; a corresponding lack of activity or only minimal activity was observed in strain TA1535 and in Escherichia coli WP2 uvrA, indicating a frameshift type of mutagenicity. Mutagenic action is based on a reduction of the nitro-function to the corresponding hydroxylamines, the penultimate mutagens, which following esterification to electrophiles apparently react with the guanine moiety of DNA to form adducts. Max mutagenic activity was observed with the trinitro-substituted compound; addition of a fourth nitro group resulted in diminished activity, presumably reflecting steric hindrance of either enzyme reduction of the nitro-function or of DNA-adduct formation. (45 Refs)

16. INDUCTION OF 6-THIOGUANINE RESISTANCE IN SYNCHRONIZED HUMAN FIBROBLAST CELLS TREATED WITH METHYL METHANESULFONATE, N-ACETOXY-2-ACETYLAMINOFLUORENE AND N-METHYL-N'-NITRO-N-NITROSOGUANIDINE.

Huang SL, Huang SM, Casperson C, Waters MD
Northrop Services, Inc., Research Triangle Park, NC, 27709
Mutat Res; 83(2):251-260 1981

The conditions required for inducing mutations in cultured, synchronized human fibroblasts were studied by examining induction of 6-thioguanine (6TG) resistance in these cells following treatment with methyl methanesulfonate (MMS; 6.25-25 ug/ml), N-acetoxy-2-acetylaminofluorene (NA-AAF; 7.5-17.5 uM), or N-methyl-N'nitro-N-nitrosoguanidine (MNNG; 5-80 uM) at different times during the G1, S, and G2 phases of the cell cycle. NA-AAF mutagenesis was dose-dependent when it occurred; NA-AAF induced no mutations during G1; but it induced an increasing frequency of mutations during S phase, with the highest frequency occurring simultaneously with the peak in DNA synthesis and the frequency declining thereafter. MMS induced mutations in treatment that included G1 and S phases and S and G2 phases, but not in the treatment that included G2 and G1 phases, indicating that mutagenesis requires DNA synthesis. Induction of mutation by MNNG followed one-hit kinetics, but mutations resulting from NA-AAF followed a higher-order function. All three chemicals resulted in an increase both in the mutation frequency and in the absolute number of mutants. Mutation in the cells studied appears to require the use of S-phase cells, regardless of the mutagenic agent used. (29 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN VERTEBRATES

17. CLASSIFICATION OF CHEMICAL AGENTS AS TO THEIR ABILITY TO INDUCE LONG- OR SHORT-PATCH DNA REPAIR IN HUMAN CELLS.

Francis AA, Snyder RD, Dunn WC, Regan JD
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 83(2):159-169 1981

The excision repair response of normal human fibroblasts (NHF) and of xeroderma pigmentosum (XP) cells to 33 chemicals was compared with that to UV irradiation (which is known to induce 'long-patch' repair of about 90 nucleotides) and to gamma irradiation (which is known to induce 'short-patch' repair of 3-4 nucleotides) by the 5-bromodeoxyuridine (BrdU) photolysis assay that quantitates unscheduled DNA synthesis. The following chemicals induced long-patch repair of 30-70 nucleotides in length and may be classified as UV-mimetic agents: N'-acetoxyacetylaminofluorene, ICR-170, 4-nitroquinoline-1-oxide, diarylcarbamate, 7-bromomethylbenzanthracene, dimethylbenzanthracene-5,6-epoxide, 7beta,8alpha-diol-9beta,10beta-epoxybenzo[a]pyrene, 7beta,8alpha-diol-9alpha,10alpha-epoxybenzo[a]pyrene, ethyl methanesulfonate, methyl methanesulfonate, and N-hydroxy-1-naphthylamine. The other chemicals elicited short-patch repair in NHF cells; the measurable DNA repair activity was at the *limit of resolution* of the sucrose density gradient technique employed to assay it. XP cells could not repair damage by these latter chemicals to the same extent that NHF cells could. It appears that, for the chemicals tested here, the ability of an

agent to elicit a long-patch DNA repair response from NHF is a property of the most active direct-acting carcinogens. (23 Refs)

18. QUANTITIVE ASPECTS OF THE FORMATION AND LOSS OF DNA INTERSTRAND CROSSLINKS IN CHINESE HAMSTER CELLS FOLLOWING TREATMENT WITH CIS-DIAMMINEDICHLOROPLATINUM(II) (CISPLATIN). II. COMPARISON OF RESULTS FROM ALKALINE ELUTION, DNA RENATURATION AND DNA SEDIMENTATION STUDIES.

Pera MF, Rawlings CJ, Shackleton J, Roberts JJ
Inst. Cancer Res., Royal Cancer Hosp., Pollards Wood Research Station, Nightingales Lane, Chalfont St. Giles, Buchinghamshire HP8 4SP, England
Biochim Biophys Acta; 655(2):152-166 1981

The formation of interstrand crosslinks in the DNA of cis-diamminedichloroplatinum(II) (cisplatin)-treated Chinese hamster cells has been demonstrated by three independent, highly sensitive techniques: namely those of alkaline elution, renaturation of crosslinked DNA and alkaline sucrose gradient velocity sedimentation. Simultaneous measurement of DNA break frequency by the first two methods and a computer model combined with the third enabled the calculation of crosslink frequency after application of low doses of cisplatin. Good agreement was found between the values obtained by the three methods used here, and also with those obtained by direct measurement of the amount of crosslinked hybrid DNA in density-labeled cells treated with higher doses of cisplatin. When measured by all three methods described here, crosslinking was found to increase during several hours after treatment and then to decrease with a half-life of between 12 and 24 hr. For low initial levels of crosslinking, this was largely attributed to an excision repair process, since the formation of breaks in DNA was only minimal. (Author abstract) (26 Refs)

19. IN VIVO AND IN VITRO ETHYLENE OXIDE EXPOSURE OF HUMAN LYMPHOCYTES ASSESSED BY CHEMICAL STIMULATION OF UNSCHEDULED DNA SYNTHESIS.

Pero RW, Widegren B, Hogstedt B, Mitelman F
Wallenberg Lab., Univ. Lund, Fack 7031, 220 07 Lund 7, Sweden
Mutat Res; 83(2):271-289 1981

Evidence of toxic exposure to ethylene oxide (EO) in factory workers producing disposable medical equipment was sought in 17 exposed women and 11 unexposed female controls from the same plant. EO exposure was 0.5-1.0 ppb for 40 hr/wk in 12 packers and 5-10 ppb for 8 hr/wk in 4 sterilizers and 1 lab technician, using the measurement of N-acetoxy-2-acetylaminofluorene (NA-AAF)-induced unscheduled DNA synthesis (UDS) in lymphocytes as the assay. The results for the controls in this study agreed with previous results for unexposed subjects: age and/or chromosome aberrations increased in a positive linear manner with increases in NA-AAF-induced UDS. However, the results for the EO-exposed packers were completely different for these two parameters: tendencies toward negative linear correlations were observed that were so divergent from controls (even for this small sample size) that these two groups were shown to be borderline significantly different populations. The data for the other group of exposed workers was nearly significantly different from that for the packers, indicating that perhaps the EO exposure in this group was not high enough to cause a significant reduction in NA-AAF-induced UDS. These results were corroborated by in vitro measurements of EO-induced (0.1-30 milliM) UDS in cultured lymphocytes: at greater than 2 milliM EO, UDS was inhibited, and even at the 0.1 milliM dose where UDS was not affected the exposed cells were sensitized to further exposure to NA-AAF, which caused a 40% cytotoxicity compared with 5% in controls. EO is toxic to lymphocytes and nontoxic doses of EO can sensitize cells to the cytotoxic action of other mutagens. (21 Refs)

20. EXCISION REPAIR OF UV-INDUCED PYRIMIDINE DIMERS IN HUMAN SKIN IN VIVO.

D'Ambrosio SM, Slazinski L, Whetstone JW, Lowney E
Coll. Medicine, Ohio State Univ., S209 Rhodes Hall, 450 West 10th St, Columbus, OH, 43210
J Invest Dermatol; 77(3):311-313 1981

The induction and loss of pyrimidine dimers in human skin in vivo was determined using UV endonuclease, alkaline sucrose sedimentation, and the fluorescent detection of nonradiolabeled DNA. The number of dimers induced following exposure of the skin to radiation emitted from a Burdick UV-800 sunlamp was quantitated by reacting the extracted DNA with Micrococcus luteus endonuclease specific for pyrimidine dimers. Exposure to 15 and 30 sec of radiation emitted from this lamp produced the formation of 12.8 and 23.6 dimers per 10(8) daltons DNA, respectively. Approx 50% of the dimers induced were lost 58 min after irradiation. Only a small percentage (less than 10) remained 24 hr postirradiation. These data partially characterize the process by which pyrimidine dimers are excised from human skin DNA in vivo. (Author abstract) (20 Refs)

21. A SIMPLIFIED METHOD FOR MEASURING SCHEDULED AND UNSCHEDULED DNA SYNTHESIS IN HUMAN FIBROBLASTS.

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Toxicology; 21(2):151-158 1981

Experiments were carried out to attempt to develop a simple, rapid method to assay unscheduled DNA synthesis (UDS) that could serve well in large-scale screening studies for carcinogenic activity. Tritium-labeled thymidine incorporation into normal human fibroblasts (HF) and into HF blocked DNA synthesis by hydroxyurea (HU) was measured in the presence of a variety of known carcinogens, precarcinogens, and noncarcinogens. Positive results (a dose-related increase in UDS in the treated inhibited cells greater than 2x that in control inhibited cells) were obtained with most of the carcinogens and negative results with most of the noncarcinogenic compounds. The method compares favorably with other more difficult and time-consuming UDS assays. (15 Refs)

22. BROMODEOXYURIDINE PHOTOLYSIS ASSAY AS A POTENTIALLY USEFUL METHOD FOR ASSESSING DNA DAMAGE AND ITS REPAIR INDUCED BY ULTRAVIOLET LIGHT.

Yatani R, Konishi T, Kusano I, Shiraishi T, Noda M, Ohashi S, Suzuki M
Dept. Pathology, Mie Univ. Sch. Medicine, Tsu, Japan
Mie Med J; 30(3):267-272 1981

The *bromodeoxyuridine (BrdUrd)* photolysis assay was used to assess DNA damage and repair induced by UV light in three melanoma cell lines, xeroderma pigmentosum (XP), normal human fibroblasts, and HeLa S3 cells. The cells were

incubated with 3H-thymidine or 14C-deoxythymidine for 24 hr, incubated in nonradioactive medium for 2 hr, then exposed to 20 Jm-2 of a 254 nanometer (nm) UV light. The cells were then incubated for 24 hr in medium containing hydroxyurea and BrdUrd or deoxythymidine. BrdUrd incorporated into DNA during the repair period by exposing the cell suspension to a 313 nm light. Postreplication repair assays were also conducted. In normal cells, a UV-induced lesion in the DNA was necessary before incubation in BrdUrd synthesized DNA to 313 nm radiation and a UV-induced lesion resulted in the incorporation of BrdUrd throughout the 3H-thymidine cellular DNA. In XP cells, the incorporation of BrdUrd into the DNA after UV-irradiation was negligible. The marked decrease in sedimentation rate seen in normal human fibroblasts after UV, BrdUrd treatment, and 313 nm irradiation did not occur in XP cells although slight differences in XP cells subjected to such treatment were seen compared with those not UV-irradiated. Normal cells became highly sensitive to 313 nm light when they were permitted to repair UV-induced lesions in the presence of BrdUrd, while XP cells did not have that sensitivity, presumably because they cannot make the initial strand breaks which necessarily precede the incorporation of BrdUrd. This assay detects excision repair as a cumulative process and estimates the patch size involved in repair replication as well as interpatch distances. (26 Refs)

23. DNA POLYMERASE ALPHA AND BETA ACTIVITY IN GAMMA-IRRADIATED HELA S3 CELLS.

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Dept. Carcinogenesis, Swiss Inst. Experimental Cancer Res., CH-1066 Epalinges s/Lausanne, Switzerland
Int J Radiat Biol; 40(2):195-204 1981

The acute effects (less than 2 hr) of gamma-irradiation on DNA polymerase alpha and polymerase beta activity in HeLa S3 cells were studied. The enzyme activities were measured in sonicates of the irradiated cells, using an exogenous DNA as template. Both DNA alpha- and beta-polymerase activities decreased following irradiation of the cells. Doses as low as 100 rad significantly reduced the activities of the enzymes. While the activities of both DNA polymerases decreased as the dose received by the cells increased, the major reduction in enzyme activity occurred with doses of 100-200 rad. The reduction in DNA alpha- and beta-polymerase activities was max by 30 min post-irradiation and recovered to control values by 2 hr post-irradiation. (Author abstract) (28 Refs)

24. EFFECT OF HYPERTHERMIA ON REPAIR OF RADIATION-INDUCED DNA STRAND BREAKS.

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Radiat Res; 87(2):314-328 1981

The effect of combined hyperthermia and ionizing radiation on the level of DNA strand breaks was studied in Chinese hamster ovary (CHO) cells. The alkaline elution technique showed that a prior hyperthermic treatment (43-45 C) rendered the cells more sensitive to the production of single strand DNA breaks by x-rays. Hyperthermia also inhibited the rejoining of DNA strand breaks; the degree of inhibition was dependent upon both temperature and duration of the treatment. The enhancement of radiation-ind uced DNA strand breaks and the inhibition of strand break repair were found to be related to the heat-induced changes in nucleoprotein composition. (27 Refs)

25. APHIDICOLIN: AN INHIBITOR OF DNA REPAIR IN HUMAN FIBROBLASTS.

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Dept. Genetics, Univ. Coll., Singleton Park, Swansea SA2 8PP, Wales
Carcinogenesis; 2(8):795-797 1981

Normal human fibroblasts and excision-deficient xeroderma pigmentosum (XP) fibroblasts were labeled in vitro with [3H]thymidine. They were then left unirradiated or exposed to 254 nanom UV. Cultures were then reincubated with media containing aphidicolin (2.5 ug/ml), an inhibitor of DNA polymerase alpha; with cytosine arabinoside (araC: 10(-4) M), an inhibitor of semi-conservative and repair replication; with both aphidicolin and araC; or neither compound. Analysis of DNA showed that UV-induced DNA single-strand breaks accumulated equally in normal fibroblasts exposed to araC or to aphidicolin. The presence of both compounds in the medium did not alter the results obtained with only one. Neither compound had any effect on the excision-deficient XP cells. The results indicate that DNA polymerase alpha does play a role in the excision repair of DNA. (14 Refs)

26. REPAIR OF DNA ADDUCTS OF THE CARCINOGEN 15,16-DIHYDRO-11-METHYLCYCLOPENTA[A]PHENANTHREN-17-ONE IN MOUSE TISSUES AND ITS RELATION TO TUMOR INDUCTION.

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Cancer Res; 41(10):4115-4120 1981

The formation and repair of DNA adducts of the carcinogen, 15,16-dihydro-11-methylcyclopenta[a]phenanthren-17-one, have been studied in three mouse tissues, liver, lung, and skin. Following a single im dose of the carcinogen, DNA adduct formation was observed in all three tissues, the highest being found in liver DNA, the tissue resistant to tumor formation by this carcinogen. In skin and lung, the tissues which were susceptible to tumor formation, binding was approx one-half that found in liver. Detailed analysis by high-pressure liquid chromatography of the adducts formed in each of the three tissues revealed no major qualitative differences in the eight adduct peaks. In vivo removal of the labeled adducts was studied over a 14-day period following initial treatment, and adducts were analyzed at each time point by high-pressure liquid chromatography. In skin and lung, active removal of the major adducts could not be measured above the normal rate of DNA turnover. By contrast, in the liver, where the rate of DNA turnover was slower, adducts were removed relatively rapidly with a half-life of approx 2.5 days. Only one minor adduct present in both skin and liver was removed more rapidly than were the major adducts. The results suggest that the persistence of carcinogen-DNA adducts coupled with a relatively high rate of cell division may be related to tissue-specific carcinogenesis by this polycyclic ketone. (Author abstract) (33 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN BACTERIA

27. GENETIC AND MOLECULAR EVENTS IN THE REPAIR OF DNA EXPOSED TO PSORALEN + NEAR-UV LIGHT IN HAEMOPHILUS INFLUENZAE.

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Biology and Agriculture Div., Bhabha Atomic Res. Centre, Bombay 400 085, India
Indian J Exp Biol; 19(2):105-111 1981

The removal of crosslinks from DNA, sedimentation properties of DNA undergoing repair, and DNA synthesis following exposure of Hemophilus influenzae cells to psoralen (P) and near-UV light (NUV) were studied. In most cases, cells were exposed to 1 ug/ml psoralen for 15 min at 37 C, then to NUV (360 nanometers) at a dose rate of 1.2 x 10(2) Joules/square meter/sec at a distance of 25 cm or a dose rate of 5.2 x 10(2) Joules/square meter/sec at a distance of 9 cm from the sample. None of the known recombination or biotransformation-defective strains were highly sensitive to PNUV, while H influenzae wild type strains were 4x more sensitive than Escherichia coli to PNUV inactivation. The rec1 gene does not have a significant role in the repair of PNUV-damaged DNA. Only KW31 and Rd (wild-type) strains were proficient in removing crosslinks; indicating that some other lesion is also important for the lethal action of PNUV. Sedimentation through alkaline sucrose gradients demonstrated that immediately after PNUV exposure cellular DNA sedimented faster than normal. Upon incubation of cells in growth medium, DNA was released from the fast-sedimenting complex and part of it sedimented at the position of control DNA. One fraction of DNA underwent strand cutting and sedimented slowly. This latter fraction disappeared after longer periods of incubation. All the DNA then sedimented at the position of untreated DNA. In the uvr2 and PS07 strains, release of DNA from fast-sedimenting material was slow. (27 Refs)

MACROMOLECULAR BINDING OF CARCINOGENS

28. EARLY EVENTS DURING LIVER CARCINOGENESIS INVOLVING TWO CARCINOGEN:PROTEIN COMPLEXES.

Blackburn GR, Andrews JP, Custer RP, Sorof S
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Cancer Res; 41(10):4039-4049 1981

This report describes the relationships between the levels of two principal carcinogen:protein complexes and histological alterations that occur during carcinogenesis in rat liver by three carcinogens. An intragastric tracer dose of N-[9-14C]-2-fluorenylacetamide interacts in normal rat liver to form the principal cytosolic 14C-carcinogen:protein complex (2S; M.W. 14,700). Continued ingestion of any of three hepatocarcinogens causes the marked loss of the 2S complex and the concurrent gain of a large-mol-wt carcinogen:protein complex (7.5S; M.W. approx 150,000) 48 hr following a dose of N-[9-14C]-2-fluorenylacetamide. The reciprocal changes in amounts of the two complexes have the following properties. The alterations occur early during hepatocarcinogenesis. In contrast to other reported early events, chemical carcinogen is directly involved. The two labeled fluorenyl proteins are the principal 14C-carcinogen:protein complexes in rat liver cytosol. Formation of the two complexes apparently involves activation of the carcinogen N-2-fluorenylacetamide. The reciprocal effects are brought on by the ingestion of any of the three hepatocarcinogens, N-2-fluorenylacetamide, 3'-methyl-4-dimethylaminoazobenzene, and ethionine. The loss of the 2S complex was previously demonstrated to be associated with the loss of the 2S protein itself (14,700-daltons polypeptide) to which the carcinogen is bound. The rate of inversion in concentrations of the two complexes is apparently related to the susceptibility of the strain and sex of rat to the carcinogen; the greater the susceptibility the more rapid is the rate. The time of the max inversion coincides approx with the appearance of putative malignant lesions. Cessation of N-2-fluorenylacetamide ingestion results in the symmetrical reversal of the reciprocal changes in the levels of the two complexes. Liver regeneration following partial hepatectomy brings about a moderate inversion of the levels of the two complexes, suggestive of the possibility that the cell proliferation associated with hepatocarcinogenesis may be casually related to the effects. Consistent with this possibility, the 2S protein has a mol wt like those of known polypeptide growth regulators. The effects on the 2S and 7.5S carcinogen:protein complexes are carcinogen group specific, inasmuch as the ingestion of any of three other types of liver carcinogens, namely, diethylnitrosamine,aflatoxin B, and thioacetamide, does not induce the reciprocal changes in the levels of the two complexes. The existence of such carcinogen group specificity suggests that chemical classes of carcinogens may be grouped on the basis of their common actions and effects on their target macromolecules. The generalizations to be derived from a classification of carcinogen group specificities seem likely to advance understanding of underlying events in chemical oncogenesis. (33 Refs)

29. THE FORMATION AND PERSISTENCE OF BENZO(A)PYRENE METABOLITE-DEOXYRIBONUCLEOSIDE ADDUCTS IN RAT SKIN IN VIVO.

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Int J Cancer; 28(3):387-392 1981

The extent of reaction of benzo(a)pyrene with DNA and the formation of benzo(a)pyrene-deoxyribonucleoside adducts in the skins of male Wistar rats were investigated. Following topical application of benzo(a)pyrene (200 nmoles), binding reached a max of 0.74 pmoles/mg DNA, 12 hr after treatment, and remained high up to 48 hr after treatment. Hydrolysis of the DNA and analysis of the deoxyribonucleoside adducts by HPLC revealed several products. The major adduct, C, (27-40% of the total adducts), co-chromatographed with deoxyribonucleoside adducts formed by reaction of (+-)7beta, 8alpha-dihydroxy-9alpha, 10alpha-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene (anti BPDE) with DNA, whilst product B, (19-23% of the total adducts), also formed in significant amounts, co-chromatographed with a further metabolite of 9-hydroxybenzo(a)pyrene bound to an as yet undetermined base in the DNA. Smaller amounts of other deoxyribonucleoside adducts, D and I, were also observed and co-chromatographed with marker compounds derived from reaction of anti BPDE with deoxyadenosine and (+-)7beta, 8alpha-dihydroxy-9beta, 10beta-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene (Syn BPDE) with DNA respectively. There was no evidence for preferential removal of any of the four adducts (B, C, D,

and I) during the 48 hr after treatment with benzo(a)pyrene. The relative resistance of rat skin, compared with mouse skin, to benzo(a)pyrene-induced skin carcinogenesis may be due in part to a lower extent of binding of benzo(a)pyrene to DNA, and a smaller percentage of both methanol-soluble hydrocarbon-deoxyribonucleoside adducts and of adducts derived from the putative ultimate carcinogen, BPDE. (Author abstract) (36 Refs)

30. SISTER-CHROMATID EXCHANGE INDUCTION IN CHINESE HAMSTER OVARY CELLS BY 8-METHOXYPSORALEN AND BRIEF PULSES OF LASER LIGHT. ASSESSMENT OF THE RELATIVE IMPORTANCE OF 8-METHOXYPSORALEN-DNA MONOADDUCTS AND CROSSLINKS.

Sahar E, Kittrel C, Fulghum S, Feld M, Latt SA
Genetics Div., Children's Hosp., Boston, MA
Mutat Res; 83(1):91-105 1981

The reaction between 8-methoxypsoralen (8-MP) and the DNA of Chinese hamster ovary cells (CHO) was promoted in a controlled manner by brief (no more than 20 nanosec), 5-14 milliJoule (mJ) pulses of near-UV laser light. A single laser pulse was sufficient to cause a significant elevation in the frequency of sister-chromatid exchanges (SCE) in CHO exposed to 0.75-1.2 x 10(-5) M 8-MP. Additional pulses, up to a total of four, stimulated more SCE production, but the increment decreased with each successive pulse. Very little additional SCE induction was observed beyond four pulses. As 8-MP concentration increased, so did the SCE frequency for a given number of laser pulses. Laser pulses of 15 mJ were more effective in inducing SCE than were 5 mJ pulses. The formation of 3H-8-MP-DNA adducts was an approx linear function of the number of laser pulses. The number of DNA crosslinks produced by 3H-8-MP increased more than linearly with the number of laser pulses. These results provide strong evidence that DNA crosslinks are not necessary for SCE induction, even with a potentially bifunctional agent. (48 Refs)

31. CARCINOGENESIS IN SYRIAN HAMSTERS BY N-NITROSO-2,6-DIMETHYLMORPHOLINE, ITS CIS AND TRANS ISOMERS, AN THE EFFECT OF DEUTERIUM LABELING.

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Dept. Pathology, Northwestern Univ. Medical Sch., 303 East Chicago Ave., Chicago, IL, 60611
Carcinogenesis; 2(8):731-735 1981

Syrian golden hamsters were divided into groups of 20 each. They were given doses of N-nitroso-2,6-dimethylmorpholine (NDMM), its cis or trans isomer, or its alpha-d4 or beta-d2 deuterium-labeled derivatives. The weekly doses (mg/kg body wt) were NDMM 18 or 50; cis-NDMM 11.5 or 31; trans-NDMM 6.5 or 17; d4 18 or 50; d2 50. A total of 52 benign and 21 malignant tumors resulted, most associated with the pancreas, liver, respiratory system, and kidneys. The survival rate among hamsters treated with cis-NDMM was about the same as the rate for those treated with NDMM. The survival rate with trans-NDMM was higher, indicating that trans-NDMM was a less potent carcinogen. Treatment with d4 produced tumors earlier than treatment with d2, suggesting that d4 was the more potent of the two. The overall incidences of malignant tumors for the NDMM, d4, and d2 groups were not significantly different. Activation to mutagenicity by pancreas microsomes, and binding to DNA of the pancreas did not differ between the isomers. (21 Refs)

32. RADIATION-SENSITIZING EFFECT OF RUBOMYCIN AND ITS COMPLEX WITH DNA.

Riabchenko NI, Smoryzanova OA, Dedenkov AN
Res. Inst. Medical Radiology, Obninsk, USSR
Med Radiol (Mosk); 26(7):46-50 1981

The radiosensitizing effect of antitumor antibiotic rubomycin (RM) and its complex with DNA was studied in C57BL mice with ip transplanted Ehrlich ascites carcinoma (EAC). On day 4 after EAC transplantation, animals were subjected to a whole-body gamma irradiation (100-500 rads); 1 hr prior to irradiation, mice were inoculated ip with RM or RM-DNA at 2, 5 and 7 mg/kg. Estimation of the specific rates of tumor cell proliferation showed that RM-DNA administration prior to irradiation provided a more effective inhibition of tumor growth than free RM or irradiation alone. (13 Refs) (In RUS)

33. METABOLISM OF CHEMICAL CARCINOGENS BY CULTURED HUMAN AND RAT BLADDER EPITHELIAL CELLS.

Autrup H, Grafstrom RC, Christensen B, Kieler J
Lab. Environmental Carcinogenesis, Copenhagen, Denmark
Carcinogenesis; 2(8):763-768 1981

Cells from human bladder epithelium cell lines HU1689, HU1752, and HU1765 and primary bladder epithelial cells from Wistar rats were exposed in vitro for 24 hr to radioactively-labeled carcinogens dissolved in the medium: [1,3,6-3H]benzo[a]pyrene (BP) 1.5 uM; [G3H]aflatoxin B1 (AFB) 1.5 uM; [14C]N-nitrosodimethylamine (DMNA) 100 uM; [ethyl-1-14C]N-nitrosoethylmethylamine (EMNA) 100 uM; and [2,5-14 C]N-nitrosopyrrolidine (NPy) 100 uM. The metabolism of the carcinogens was assayed by the release of metabolites into the culture medium and the binding of radioactive metabolites to DNA. The human bladder cells retained the capacity to metabolize chemical carcinogens. Binding of DNA occurred to a similar extent in all three cell lines. More BP was bound to DNA in human bladder cells than in rat bladder cells. More than 90% of the metabolites of BP in human cells consisted of organo-soluble products, primarily the 9,10-and 7,8-BP diols. N-nitrosamine metabolism produced CO2. NPy was oxidized in both the alpha and beta positions, predominantly alpha in human cells. EMNA was apparently metabolized, but did not bind to DNA. The results suggest that the human bladder may be able to activate carcinogens that come into direct contact with the epithelium, and that it utilizes pathways that are different from those found in other tissues and cells. (38 Refs)

34. OPTICALLY DETECTED MAGNETIC RESONANCE EVIDENCE FOR CARCINOGEN-NUCLEIC ACID INTERACTION IN THE TETRAHYDRO-9,10-EPOXYBENZO[E]PYRENE-DNA ADDUCT.

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J Am Chem Soc; 103(17):5257-5259 1981

The carcinogenic action of polycyclic aromatic hydrocarbons evidently is mediated by metabolically-activated intermediates which bind covalently to DNA. The optically-detected magnetic resonance technique was used to study the structure of the adduct of tetrahydro-9,10-epoxybenzo[e]pyrene (BePE) with DNA. The pyrene triplet chromophore in the BePE-DNA adduct appears to exist in an environment intermediate between complete intercalation and complete solvent exposure. (21 Refs)

EFFECT OF CARCINOGENS ON MACROMOLECULAR SYNTHESES

35. COMPARISONS OF THE EFFECTS OF CHEMICAL CARCINOGENS IN MIXED CULTURES OF RAT HEPATOCYTES AND HUMAN FIBROBLASTS.

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Dept. Pathology, Duke Univ. Medical Center, Durham, NC, 27710
Carcinogenesis; 2(8):709-715 1981

Human male diploid fibroblasts (strain GM 3468) and parenchymal hepatocytes from male Sprague Dawley rats were treated separately and in mixed cell cultures with benzo[a]pyrene (BP), diethylnitrosamine (DEN), or 2-acetylaminofluorene (AAF). Fibroblast DNA was prelabeled with 5-bromo-2'-deoxyuridine. After exposure to the carcinogens, fibroblast and hepatocyte DNA was analyzed for unscheduled DNA synthesis (UDS). Fibroblast and hepatocyte DNA from mixed cultures was separated by isopycnic centrifugation in neutral cesium chloride. The hepatocarcinogens DEN and AAF produced increased UDS in hepatocytes, but not in fibroblasts, either separately or in mixed cultures. BP, a non-hepatocarcinogen, produced more UDS in in fibroblasts than in hepatocytes in mixed cultures. More BP was bound to fibroblast DNA than to hepat ocyte DNA. BP bound to DNA from cultures of fibroblast alone was abou 30% of that bound to fibroblast DNA from mixed cultures. BP produced no UDS in fibroblast in the absence of hepatocytes. Evidently the hepatocytes activated the UDS-promoting capacity of BP, which then was passed to the fibroblasts. The results obtained with BP, DEN, and AAF correspond to previous in vivo observations of the tissue-specific carcinogenicity of the three agents. The possibility that intercellular distribution may play a role in carcinogenic effects is indicated. (37 Refs)

36. THE RESPONSE OF L5178Y-R AND L5178Y-S CELLS TO X RAYS UNDER OXIC AND HYPOXIC CONDITIONS.

Szumiel I, Budzicka E, Niepokojczycka E, Wlodek D, Beer JZ
Dept. Radiobiology and Health Protection, Inst. Nuclear Res., PL-030195 Warsaw, Poland
Radiat Res; 87(3):592-601 1981

The oxygen effect on two strains of murine lymphoma cells, L5178Y-R and L5178Y-S, which are inversely cross-sensitive to x-rays and UV light, was studied and the phenomena following x-ray exposure under oxic and anoxic conditions were compared. Both cells strains were less sensitive to x-rays under hypoxia; hypoxic conditions affected the survival of both strains to the same degree. Under oxic conditions, exposure to x-rays affected DNA synthesis more markedly in L5178Y-S cells than in L5178Y-R cells. Under hypoxic conditions, [3H]deoxythymidine incorporation was not affected by irradiation in either of the cell strains. Thus, in the case of L5178Y-S cells, a clear difference could be seen between the incorporation rates at the same survival level under oxic and hypoxic conditions. During incubation of L5178Y-S cells irradiated under oxic conditions, a shift occurred toward DNA contents apparently higher than that characteristic for the control G2 cells. This was particularly evident in the 21-hr sample. The normal distribution was once again observed in the 72-hr sample. Under hypoxic conditions, DNA content distribution was less disturbed by irradiation and remained close to the normal one during the postexposure incubation. The results seem to be compatible with the assumption that the rejoining of single-stranded breaks is slow in L5178Y-S cells. (29 Refs)

37. ELECTRON MICROSCOPY OF AD5 REPLICATING MOLECULES AFTER IN VIVO PHOTOCROSSLINKING WITH TRIOXSALEN.

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Virology; 114(1):60-70 1981

A new approach for studying replicating DNA structures is presented. Ad5 replicative intermediates were fixed in vivo by reducing DNA interstrand crosslinks with 4,5',8-trimethylpsoralen and near UV light (365 nm) in order to maintain the structure of replicating DNA molecules and to prevent branch migration which may occur during the isolation and analysis of these molecules. The replicating Ad5 material was analyzed under neutral and denaturing conditions by electron microscopy. The in vivo crosslinking followed by a mild extraction of nuclei allowed intact replicating molecules to be isolated. In this way all branch positions characteristic for the first round of replication were observed. Furthermore, a statistical analysis of more than a hundred molecules with multiple single-stranded branches visualized by electron microscopy showed that growing points move from one end of the Ad5 molecule toward the other one and not in opposite directions. Crosslinking of the duplex part of the replicating molecules made it possible to visualized these structures for the first time under denaturing conditions. The direction of DNA synthesis at the growing points can be specified and replication is shown to occur continuously. (Author abstract) (24 Refs)

38. FAILURE TO DISCRIMINATE INITIATION FROM PROMOTION OF LIVER TUMORS IN A LONG-TERM STUDY WITH THE PHENOBARBITAL-TYPE INDUCER ALPHA-HEXACHLOROCYCLOHEXANE AND THE ROLE OF SUSTAINED STIMULATION OF HEPATIC GROWTH AND MONOOXYGENASES.

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Cancer Res; 41(10):4140-4146 1981

The compound alpha-hexachlorocyclohexane (alpha-HCH) was administered po to female Wistar rats for periods of up to 33 mo; doses were 20 mg/kg/day, 200 mg/kg every 2nd wk, or 420 mg/kg every 3rd wk. Increases of liver size, DNA, RNA, and protein (by 50 to 100%) and of drug-metabolizing enzyme activities (up to 300%) observed previously after single doses of alpha-HCH were found to persist after approx 1/3, 1, and 2 yr of treatment. At 1 and 2 yr, DNA synthesis was measured by [3H]thymidine uptake and was no higher than in controls. All changes regressed upon withdrawal of alpha-HCH after 1 yr of treatment. These findings provide no evidence to suggest a protracted development of toxicity or of growth autonomy in the majority of liver cells. Foci of altered cells, neoplastic nodules, and in 2 animals hepatocellular carcinoma were detected histologically in the livers of 24 of 34 treated rats. In livers of 10 of 22 untreated control rats, foci of altered cells developed 'spontaneously' between 12 and 34.5 mo. If neoplastic lesions were induced by a single dose of diethylnitrosamine, 75 or 150 mg/kg, subsequent treatment with alpha-HCH led to the appearance of hepatocellular carcinoma within 7 mo. Altogether, hepatocellular carcinomas were found in 18 of 21 rats treated with both agents but in only 3 of 26 animals treated with diethylnitrosamine alone. The results show that determination of tumor numbers alone in a long-term animal experiment does not allow one to decide whether alpha-HCH (and similar 'xenobiotic inducers') is an initiating

carcinoge n or merely promotes tumorigenesis from 'spontaneous' lesions. Our findings support the latter possibility by the failure to detect evidence suggesting initiating potential of alpha-HCH, by the enhanced mitotic response to alpha-HCH in foci of altered cells as reported elsewhere, and by the observation of a permanent stimulatory action on liver growth during prolonged exposure to alpha-HCH. (Author abstract) (46 Refs)

39. EFFECTS OF 3-ISOBUTYL-1-METHYLXANTHINE AND CYCLIC NUCLEOTIDES ON THE BIOCHEMICAL PROCESSES LINKED TO SKIN TUMOR PROMOTION BY 12-O-TETRADECANOYLPHORBOL-13-ACETATE.

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Cancer Res; 41(10):3927-3935 1981

The phosphodiesterase inhibitor 3-isobutyl-1-methylxanthine (IBMX), which enhances 12-O-tetradecanoylphorbol-13-acetate (TPA)-stimulated cyclic nucleotide levels and ornithine decarboxylase (L-ornithine carboxy-lyase, EC 4.1.1.17) activity in mouse epidermis in vivo, was tested for its ability to modify the process of skin carcinogenesis using the initiation-promotion (two-step) model system for the production of skin tumor in mice. Topical application of 10 umol of IBMX prior to each promotion with 8.5 nmol of TPA reduced by 78% the number of papillomas per mouse. The inhibition was dose dependent. All phosphodiesterase inhibitors tested inhibited the development of skin papillomas. Topical applications of guanosine cyclic 3':5'-monophosphate and/or adenosine cyclic 3':5'-monophosphate before each treatment with TPA were also very effective in inhibiting the formation of skin papillomas. Combined treatments including IMBX, guanosine cyclic 3':5'-monophosphate and adenosine cyclic 3':5'-monophosphate reduced by 98% the incidence of skin papillomas promoted by TPA. However, IBMX treatment 24 hr after each promotion with TPA did not suppress the formation of skin papillomas. Futhermore, repeated applications of IBMX before or after initiation with 7,12-dimethylbenz[a]anthracene did not alter the development of skin tumors. These results indicate that phosphodiesterase inhibitors and cyclic nucleotides inhibit the promotion of skin papillomas. Indeed, these modifiers act on some of the biochemical events proposed to be necessary components of the carcinogenesis process. They inhibit dramatically both TPA-increased polyamine levels and TPA-stimulated RNA, protein, and DNA synthesis. Combined treatments including IBMX and cyclic nucleotides produced additive inhibitions of polyamine, RNA, protein, and DNA synthesis in relation with their greater reduction of the formation of skin papillomas. Since IBMX and cyclic AMP block the usual accumulation of putrescine and spermidine produced by TPA in mouse epidermis in vivo and inhibit the activity of ornithine decarboxylase when added in the assay mixture, these compounds may actually interact directly with the enzyme in situ as other ornithine decarboxylase inhibitors do. (Author abstract) (50 Refs)

40. DIFFERENCE IN GENETIC EXPRESSION BETWEEN NORMAL AND TRANSFORMED WI-38 CELLS.

Nose K, Okamoto H, Namba M
Dept. Biochemistry, Toyama Medical and Pharmaceutical Univ. Sch. Medicine, Sugitani, Toyama, Japan
Cell Struct Funct; 6(2):93-101 1981

In order to study transformation-specific gene expression, total poly(A)+RNA was extracted from normal WI-38 and Co60-irradiation-transformed WI-38 (CT-1) human diploid fibroblasts, complementary DNA (cDNA) against this RNA was prepared, and hybridization studies of these two nucleic acids were performed; also, radiolabeled proteins from the normal and transformed cells were prepared and examined by two-dimensional gel electrophoresis. Poly(A)+RNA sedimenting from 5S to 23S was hybridized to cDNA fractions greater than 150 bases (av size: 300 bases) in two combinations: homologous (both nucleic acids came from the same cell type) and heterologous (the RNA and DNA came from opposite cell types); considerable hybridization occurred in both cases, showing that there is extensive homology between the poly(A)+RNAs of normal and transformed cells. Approx 200 protein spots were examined electrophoretically from both cell types, first by isoelectrofocusing and then by sodium dodecyl sulfate-polyacrylamide gel analysis followed by autoradiography: two proteins were found in the normal cells that were not present in the transformed cells, and two proteins were found in the transformed cells that were not found in the normal cells. These results indicate that transformation of human fibroblasts is accompanied by only limited alteration in genetic expression. (25 Refs)

41. DNA REPLICATION IN X-IRRADIATED HUMAN LYMPHOCYTES.

Agarwal SS, Katz EJ, Krishan A, Loeb LA
(c/o Loeb) Dept. Pathology SM-30, Univ. Washington Sch. Medicine, Seattle, WA, 98195
Cancer Res; 41(10):3973-3978 1981

Human peripheral blood lymphocytes are well-differentiated cells. Ordinarily, they do not divide and are considered to be in the Go stage of the cell cycle. These cells can be stimulated to undergo DNA replication in culture by mitogens such as phytohemagglutinin. In the present study, we have examined cellular and biochemical events that occur after exposure of lymphocytes to x-irradiation. Irradiation with up to 100 rads, prior to stimulation with phytohemagglutinin, did not interfere with DNA replication. At later periods, DNA replication was inhibited proportional to the amount of radiation. In comparison to DNA synthesis, the effect of x-irradiation on RNA and protein synthesis in phytohemagglutinin-stimulated lymphocytes was less marked. Furthermore, x-rays did not inhibit either the induction or the continual synthesis of DNA polymerase-alpha or -beta in response to phytohemagglutinin. Kinetic studies wit h different nucleotide substrates suggest that cellular pools of nucleotides are not significantly altered by x-irradiation. Thus, the inhibition of DNA synthesis in irradiated cells is likely to be due to damage to the cellular DNA template. The inhibition of DNA synthesis was accompanied by accumulation of cells in the G2 and M stages of the cell cycle, suggesting that inhibition of DNA replication by x-irradiation is a postmitotic event. (Author abstract) (38 Refs)

REVIEWS

42. THE ROLE OF GENETIC TOXICOLOGY IN A SCHEME OF SYSTEMATIC CARCINOGEN TESTING.

Williams GM, Weisburger JH, Brusick D
Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
ACS Symp Ser; 160:57-87 1981

No single test has been developed for detecting all hazardous chemicals. It is therefore important to formulate the criteria for selecting the best combination of tests for a test battery. A bat-

tery should combine detection and confirmation of a hazard in one step. It should be capable of including all types of hazards. The tests should have clear biological significance and should maximize metabolic parameters. The Decision Point Approach involves five sequential steps in evaluating the carcinogenic potential of a chemical. First the structure of the chemical is determined. Then a series of in vitro short-term tests are run. These tests include bacterial mutagenesis, DNA repair, mammalian mutagenesis, sister chromatid exchange, and cell transformation. The evidence provided by the tests is evaluated. A suspected chemical is tested in limited in vivo assays for skin tumor induction in mice, pulmonary tumor induction in mice, breast cancer induction in female Sprague-Dawley rats, and altered foci induction in rodent liver. Further evaluation is made. Chronic bioassays complete the series of tests. A final evaluation of all the tests is made, allowing a decision to be made on the hazard of the chemical in question. (63 Refs)

43. TWO INDEPENDENT ASPECTS OF TUMOR PROMOTION.

Berenblum I, Armuth V
Weizmann Inst. Science, Rehovot, Israel
Biochim Biophys Acta; 651(1):51-63 1981

The possibility of separate and independent mechanisms of tumor promotion is explored based on a review of evidence for sites of action within the cell. The multi-stage theory of carcinogenesis is presented. Evidence for two types of promoting action is discussed: that operating at the regulator-gene level and that operating at the level of the cell-surface membrane. Tumor promotion is generally regarded as an epigenetic phenomenon in an initiated cell which permits the phenotypic expression of an altered genotype. Since an influence on the cell's mutation rate or its repair mechanisms would need to operate close in time to initiation, these mechanisms are not widely regarded as likely. Growing evidence suggests that pro motion may proceed by the derepression of a neighboring regulator gene brought about by the action of some newly synthesized tumor-specific protein(s). Cell membranes in general and cell-surface membranes in particular have an important role in regulating cellular functions, and a great variety of changes in cell-surface membranes is known to effective in this regard. Lack of cell adhesiveness and of contact inhibition in neoplastic cells have long been recognized as cell-surface phenomena. There is evidence that promoters, particularly phorbol ester promoters, can bind to cell-surface membranes and alter their properties. Induction of plasminogen activator, prostaglandins, enzymes of polyamine biosynthesis, and alterations in cyclic nucleotide levels are known cytoplasmic effects of promoter action. Implications and interrelations of these findings are discussed. (224 Refs)

44. EXPERIMENTAL APPROACHES TOWARDS THE BIOCHEMICAL ANALYSIS OF CHEMICAL CARCINOGENESIS.

Laishes BA
McArdle Lab. for Cancer Res., Univ. Wisconsin Medical Sch., Madison, WI, 53706
ACS Symp Ser; 160:197-215 1981

Developments in chemical carcinogenesis research as they affect the understanding of malignancy at the molecular level are reviewed. Early observations noted the relationship between exposure of humans to certain substances and the occurrence of certain cancers. This led to laboratory experiments demonstrating the induction of cancers in animals by purified chemicals. Carcinogenesis was further depicted as a two-stage process. The first step involved initiation of cancer potential in cells by a carcinogen. The second step involved promotion of cancer development by a promoting substance that might be different from the initiator. The importance of the presence of various antagonistic carcinogens, enzymes, and metabolites of carcinogens was recognized as affecting the development of cancer or the lack of it. Molecular analysis showed that carcinogens are electrophilic molecules that bind to the DNA molecules in target cells. Current research is exploring the importance of cell cycle phase on carcinogenesis. Cell lineage and genotypic cell markers are being studied as tools for cancer research. (91 Refs)

45. CYTOTOXIC AND CLASTOGENIC EFFECTS OF SOLUBLE AND INSOLUBLE COMPOUNDS CONTAINING HEXAVALENT AND TRIVALENT CHROMIUM.

Levis AG, Majone F
Inst. Animal Biology, Univ. Padua, Padua, Italy
Br J Cancer; 44(2):219-235 1981

Cr(III) and Cr(VI) compounds of varying solubilities have been tested in vitro for their ability to inhibit cell growth and nucleic acid and protein syntheses in BHK cells, to induce alterations in the mitotic cycle in HEp cells, and to increase the frequency of chromosomal aberrations and sister chromatid exchanges (SCE) in CHO cells. All Cr(VI) compounds, and particularly those containing soluble Cr (VI), such as potassium dichromate and zinc yellow, differentially inhibit macromolecular syntheses in BHK cells, that of DNA being always the most affected. Among Cr(III) compounds, which generally have very low cytotoxicity, chromite is particularly active, and inhibits cell growth and DNA synthesis even more than the poorly soluble Cr(VI) compounds. Preincubation in growth medium, with or without metabolizing cell cultures, solubilizes considerable amounts of Cr(VI) from zinc yellow and chromite, but significant amounts are also obtained from the most insoluble Cr(VI) pigments. When BHK cells are treated with such preincubated solns, reduction of soluble Cr(VI) to Cr(III) by cell metabolites is seen with all Cr(VI) compounds, accompanied by decreased cytotoxicity. The same differences between Cr(VI) and Cr(III) compounds apply to the cytotoxic effects on mitosis of HEp cells and the clastogenic effects on CHO cells. The activity of chromite, the only Cr(III) pigment capable of significantly increasing the frequency of SCE, is due to contamination with soluble Cr(VI). In contrast to the very low cytotoxicity of Cr(III), much higher chromium levels are detected in the cells incubated with soluble Cr(III) than with the same concentrations of soluble Cr(VI). 50% and 75% of chromium accumulated in the cells during treatments with Cr(VI) and Cr(III) respectively remains firmly bound to the cells, even when they are incubated for up to 48 hr in normal growth medium. Chromium accumulated in the cells after treatment with Cr(III) is most probably bound to the cell membrane, whereas some of the Cr(VI) is transported through the cell membrane and reduced in the cell nucleus. The results of the present investigation are in agreement with those obtained with the same Cr(VI) and Cr(III) compounds in mutagenicity assays in bacteria and carcinogenicity tests in rodents. A re-evaluation of the mechanisms of chromium carcinogenesis is proposed. (Author abstract) (54 Refs)

46. ANTIBODIES TO CARCINOGENS-DNA ADDUCTS.

Poirier MC
Lab. Experimental Pathology, NCI, NIH, Bethesda, MD, 20205
JNCI; 67(3):515-519 1981

The preparation of rabbit antibodies to carcinogen-DNA adducts, the sensitivity and specificity of the antibodies, and their uses in studying carcinogen binding in rat tissues and cell cultures are reviewed. Among the areas currently under investigation by radioimmunoassay are the nature and extent of carcinogen binding to liver and kidney DNA in rats fed 2-acetylaminofluorene and the determination and manipulation of DNA adducts in cultured cells exposed to N-acetoxy-2-acetylaminofluorene. Solid-phase immunoassays may make it possible to measure adducts in a single cells, and direct visualization of adducts on DNA by electron microscopy may enable the localization of a carcinogen with respect to proximity of single-strand gaps, repair patches, or replication complexes. (11 Refs)

47. THE DEVELOPMENT AND VALIDATION OF MUTAGENICITY SCREENING TESTS.

Durkin PR, Santodonato J
Center for Chemical Hazard Assessment, Syracuse Res. Corporation, Merill Lane, Syracuse, NY, 13210
Tappi; 64(9):153-159 1981

Development of short-term tests for mutagenicity screening and the problems involved in their use for predicting carcinogenic hazard to humans are reviewed. Five groups of tests are described: (1) mutagenesis in microorganisms (eg Salmonella/Ames test, Escherichia coli K-12 reversion and forward mutation tests), (2) mutagenesis in mammalian cells (eg primary or early passage Syrian hamster embryo cells and cultured Chinese hamster V79 cells), (3) DNA damage/repair tests and DNA replication inhibition (eg unscheduled DNA synthesis in human skin and foreskin fibroblasts and in human Hela cells), (4) cytogenetic tests in vitro (eg chromosome aberrations in Chinese hamster cells and in cultured human lymphocytes), and (5) in vitro cell transformations (eg primary and early passage Syrian hamster embryo cells). The inability to validate mammalian bioassays or in vitro screening tests with human data complicates environmental toxicology and protection of the human environment. Acting only after a compound has been shown to be a human carcinogen is tantamount to experimenting with the human population. However, the economic consequences of over-regulation are clearly undesirable. Short-term tests by themselves do not constitute definite evidence of carcinogenic threat to humans, but positive responses are considered suggestive evidence. (90 Refs)

48. SHORT-TERM TEST SYSTEMS FOR POTENTIAL MUTAGENS AND CARCINOGENS: I. MICROBIAL TESTS (ONCOLOGY OVERVIEW).

International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Short-Term Test Systems for Potential Mutagens and Carcinogens: I Microbial Tests (Oncology Overview) Simmon, V F; Peirce, V; eds This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-922903:; OK-81/03:124pp. 1981

Oncology Overviews are a service of the International Cancer Research Data Bank (ICRDB) Program of the National Cancer Institute. They are retrospective bibliographies containing 100-500 selected abstracts of published research on topics of high interest to cancer investigators. This Oncology Overview addresses itself to the development and direct application of short-term, rapid tests or assays in prokaryotic and lower eukaryotic microorganisms which screen for the carcinogenicity or mutagenicity of chemicals and other agents. This scope covers the experimental designs and specificities, modifications and improvements in methodologies, and selections of test vehicles for short-term assays. In addition to reviewing the development of standard procedures, this Overview includes the development of reporting standards for mutagen and carcinogen tests. The review or evaluation of test systems is also covered. This Oncology Overview specifically excludes studies in which the use of short-term test systems appears, more or less, to be incidental to investigations of the molecular mechanism of carcinogen metabolism, activation, DNA alteration, or the binding of carcinogens to macromolecules.

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De Fernicola NA, De Azevedo FA
Divisao de Toxicologia e Ecotoxicologia, Diretoria de Tecnologia e Desenvolvimento, Sao Paulo, Brazil
Rev Bras Saude Ocup; 33(9):62-68 1981
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2. EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.
International Agency for Research on Cancer
International Agency for Res. on Cancer, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum; 26:1-411 1981

3. STUDIES ON THE ROLE OF ORAL CONTRACEPTIVE USE IN THE ETIOLOGY OF BENIGN AND MALIGNANT LIVER TUMORS.
Mettlin C, Natarajan N
Cancer Control and Epidemiology, Rosewell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Surg Oncol; 18(1):73-85 1981

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4. EXPERIMENTAL RADIATION CARCINOGENESIS: WHAT HAVE WE LEARNED?
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Hashizume T
Div. Physics, National Inst. Radiological Sciences, 9-1 Anagawa 4-Chome, Chiba Shi 260, Japan
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Dept. Preventive Medicine, Div. Environmental Toxicology, Univ. Texas Medical Branch, Galveston, TX, 77550
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Zh Eksp Klin Med; 21(3):287-292 1981
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Cancer Forum; 5(1):4-14 1981

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Pediatric Oncology Branch, Div. Cancer Treatment, NCI, NIH, Public Health Service, United States Dept. Health and Human Services, Bethesda, MD, 20205
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Res. Lab. Experimental Immunobiology, Moscow, USSR
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28. ANIMAL MODELS OF INTRA-ORAL CHEMICAL CARCINOGENESIS: A REVIEW.
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J Oral Pathol; 10(3):129-146 1981

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MECHANISMS OF CARCINOGENESIS

Macromolecular Alteration and Repair

SERIES CK11 No. 82/02

FEBRUARY, 1982

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BIOLOGICAL ASPECTS OF DNA ALTERATION AND REPAIR IN RELATION TO CARCINOGENICITY

1. ACTIVATION OF RELATED TRANSFORMING GENES IN MOUSE AND HUMAN MAMMARY CARCINOMAS.

Lane MA, Sainten A, Cooper GM
Sidney Farber Cancer Inst., Boston, MA, 02115
Proc Natl Acad Sci USA; 78(8):5185-5189 1981

High mol wt DNAs of five tumors induced by mouse mammary tumor virus (MMTV), two mouse mammary tumors induced by a chemical carcinogen, and one human mammary tumor cell line (MCF-7) were ass ayed for the presence of transmissible activated transforming genes by transfection of NIH 3T3 mouse cells. DNAs of all five MMTV-induced tumors, one chemical carcinogen-induced tumor, and the human tumor cell line induced transformation with high efficiencies (approx 0.2 transformant per ug of DNA). NIH cells transformed by DNAs of MMTV-induced tumors did not contain exogenous MMTV DNA sequences, indicating that MMTV-induced mammary carcinomas contained activated cellular transforming genes that were not linked to viral DNA. The transforming activities of DNAs of all five MMTV-induced tumors, the chemical carcinogen-induced mouse tumor, and the human tumor cell line were inactivated by digestion with the restriction endonucleases Pvu II and Sac I, but not by BamHI, EcoRi, HindIII, Kpn I, or Xho I. These results indicate that the same or closely related transforming genes were activated in six different mouse mammary carcinomas, induced by either MMTV or a chemical carcinogen, and in a human mammary carcinoma cell line. (Author abstract) (25 Refs)

2. CHARACTERIZATION OF HUMAN CELLS TRANSFORMED BY CHEMICAL AND PHYSICAL CARCINOGENS IN VITRO.

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Dept. Physiological Chemistry, Coll. Medicine, Ohio State Univ., 333 W. 10th Ave., Columbus, OH, 43210
In Vitro; 17(8):719-729 1981

Several different classes of chemical carcinogens induced the transformation of human fibroblasts grown in vitro. Characteristics of the events that occur from time of treatment through the expression of neoplastic transformation are presented. The S-phase appeared to be the portion of the cell cycle most vulnerable to insult. Staging of the cells by blocking them in G1 before releasing them to proceed through scheduled DNA synthesis (S) was required to induce reproducible transformation. Compounds such as insulin were added to the cells upon release from the block to sensitize the cells to the carcinogen that was added during S. Growth of the transformed cells as distinct from nontransformed cells was promoted by growth in medium supplemented with 8X nonessential amino acids. Carcinogen-treated cells in the early stage of transformation exhibited abnormal colony morphology and were able to grow at 41 C, in air atmosphere, and in medium supplemented with only 1% serum. In addition, the transformed cells were insensitive to KB cell lysate and exhibited density independent, as well as anchorage independent, growth (ie, growth in 0.33% agar). Cells that grew in soft agar also produced undifferentiated mesenchymal tumors in preirradiated nude mice. (Author abstract) (19 Refs)

3. XERODERMA PIGMENTOSUM AND MEDULLOBLASTOMA: CHROMOSOMAL DAMAGE TO LYMPHOCYTES DURING RADIOTHERAPY.

Giannelli F, Avery J, Polani PE, Terrell C, Giammusso V
Pediatric Res. Unit, Guy's Hosp., London SE1, England
Radiat Res; 88(1):194-208 1981

The response of a xeroderma pigmentosum (XP) patient to radiotherapy for medulloblastoma (MB) was evaluated in terms of clinical and cytogenetic observations. Two other children with MB alone were treated similarly on the linear accelerator following surgery. Treatment was started to the whole cranium, reduced to cover the posterior fossa and pituitary region, and then finally reduced to cover the posterior fossa alone. The dose to the posterior fossa was the highest (5,000, 5,500 rad). In the two MB patients, spinal radiation was not begun until 2,000-2,500 rad of cranial radiation had been administered, while in the XP patient, spinal irradiation was begun immediately. Mild radiation erythema was observed in all three patients at the end of radiotherapy. The total WBC and platelet counts of the XP patient did not at any time, fall too low for daily treatment as they did in the Asian MB patient. The XP patient was alive and neurologically well 2.5 yr after treatment. At the end of treatment, the chromosome aberrations per rad were lowest in the XP patient and highest in one of the MB patients. Results indicated that the number of chromosome aberrations is much better correlated to spinal than cranial irradiation doses. It was suggested that since the XP patient had received treatment most damaging to lymphocytes (spinal radiation) partly at the beginning and partly at the end of radiotherapy, the final chromosome damage may be lower since a great proportion of the damaged cells may have been lost during therapy. The results of this study indicated that radiotherapy administered to XP patients does not produce high frequencies of damaged lymphocytes, high levels of chromosome aberrations per cell, nor clinically abnormal reactions. (30 Refs)

4. SENSITIVITY AND RESISTANCE OF HUMAN MELANOMA CELLS TO ULTRAVIOLET RADIATION.

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Dept. Biochemistry, Univ. Queensland, Brisbane 4067, Australia
Aust J Exp Biol Med Sci; 59(4):515-520 1981

A human melanoma cell line (MM253) was found to be sensitive to UV radiation, having a Do of 1.0 J/m2 when cloned on plastic culture dishes and a Do of 2.3 J/m2 when cloned in agar. These figures are much lower than those obtained for all other human melanoma cell lines studied in this laboratory (Do of 32-40 J/m2) and demonstrate that MM253 is unusually UV sensitive. The increased level of UV sensitivity in MM253 is not due to a reduced capacity for excision of pyrimidine dimers, repair of DNA single-strand breaks or elongation of newly-synthesized DNA strands when comparison is made with a UV-resistant melanoma cell line. (Author abstract) (11 Refs)

5. INDUCTION OF GENE MUTATION IN AND CELL TRANSFORMATION OF MAMMALIAN CELLS BY MODIFIED PURINES: 2-AMINOPURINE AND 6-N-HYDROXYLAMINOPURINE.

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Proc Natl Acad Sci USA; 78(9,part2):5685-5689 1981

A classical mutagen in prokaryotic systems, 2-Aminopurine is inactive as a carcinogen in two animal species. To determine the basis for this discrepancy in the correlation between carcinogenesis and mutagenesis, the ability of 2-aminopurine to induce somatic mutation and neoplastic transformation concomitantly in the same cellular system was examined. 6-N-hydroxylaminopurine, a related modified purine that is a mutagen and a carcinogen, was also studied. 2-Aminopurine was a mutagen in Syrian hamster embryo cells, but its activity was very weak. The max induced mutation frequency with either of two mutational markers was only 7 x 10(-6) mutants per surviving cell. 2-Aminopurine also induced morphological transformation of the cells under the same conditions, but the frequency was only approx 0.04% per surviving colony. Neoplastic transformation of the cells after 2-aminopurine treatment was not observed in these experiments. These resuits indicate that 2-aminopurine is, at best, a weak transforming agent. The lack of carcinogenic activity in vivo with 2-aminopurine is consistent with these observations. In contrast to the results with 2-aminopurine, 6-N-hydroxylaminopurine was very effective mutagen in these cells (up to 10(-3) mutants per survivor) and induced morphological transformation of the cells in a dose-dependent manner. Furthermore, neoplastic transformation was induced by this nucleic acid base analog, the correlation of mutagenic activity with transforming ability of these two modified purines supports a relationship between mutagenesis and carcinogenesis. However, relative to other carcinogens, there is a quantitative difference in the ability of 6-N-hydroxylaminopurine to induce cell transformation and mutation. For example, in benzo[a]pyrene-treated cultures, the ratio of the frequency of induced morphological transformation to that of somatic mutation was approx 100, whereas for 6-N-hydroxylaminopurine-treated cultures, the ratio of transformation to mutation was only 3-12.5. This indicates that 6-N-hydroxylaminopurine is less potent than benzo[a]pyrene in inducing transformation when compared at equal mutagenic potency. This is consistent with our hypothesis that cell transformation, and possibly cancer, occurs predominantly as the result of a mutation at the chromosome level ratner than a gene mutation. (Author abstract) (27 Refs)

BIOLOGICAL ASPECTS OF DNA ALTERATION AND REPAIR IN RELATION TO MUTAGENICITY

6. THE MUTAGENIC EFFECT OF CIS-DIAMMINEDICHLOROPLATINUM II AND ITS DEGRADATION PRODUCTS IN THE AMES MICROBIAL ASSAY.

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Environ Mutagen; 3(5):555-563 1981

The Ames microbial mutagenicity assay was used to test the mutagenicity of cis-diamminedichloroplatinum (II) (cis-DDP) and its degradation products (obtained from a soln aged for 12 mo at 37 C), platin B salt, magnus red, and magnus red anion salt in order to determine if the positive mutagenic response of the platinum compound could be due to, or enhanced by, the presence of degradation products. A significant increase in hist+-revertants occurred with Salmonella strains TA98, TA100, TA92, and TA94 with platin B salt, magnus red, magnus red anion salt, and lyophilized cis-DDP. The aged cisplatin, however, exhibited an increase only with strains TA100, TA92, and TA94. All degradation products exhibited a slight but significant mutagenic effect with strains TA1535 and TA1537. The mixed function oxidase activation system was required for mutagenicity only in the positive control ethidium bromide. These results indicate that platinum degradation complexes are weak mutagens which can induce both base pair and frameshift-type mutations. (32 Refs)

7. MUTAGENICITY, TUMORIGENICITY, AND ELECTROPHILIC REACTIVITY OF THE STEREOISOMERIC PLATINUM(II) COMPLEXES OF 1,2-DIAMINOCYCLOHEXANE.

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Cancer Res; 41(11,part1):4368-4377 1981

Without external activation, cis- and trans-dichlorodiammineplatinum(II) and the cis, trans(-), and trans(+) forms of dichloro-1,2-diaminocyclohexaneplatinum(II) (DDCP) and sulfato-1,2-diaminocyclohexaneplatinum(II) (SHP) showed a 400-fold range of mutagenicity for Salmonella typhimurium TA100 and TA98; they were 2 to 10x more mutagenic for strain TA100 than for strain TA98. With strain TA100, trans-DDP was less than 0.5% as mutagenic as the cis isomer, which produced 180 revertants/nmol. For the diaminocyclohexane complexes, mutagenic activity was strongly dependent on the stereoisomer of the diaminocyclohexane in the complex. Thus, with strain TA100, the trans(+) forms of DDCP and SHP produced 220 and 66 revertants/nmol, respectively, while the cis- and trans(-) isomers induced only 10 and 5% as many revertants as the trans(+) forms. The SHP complexes were the most reactive toward DNA and produced a greater reduction in the transforming activity of Bacillus subtilis DNA after 3-hr reaction times than did the DDP or DDCP complexes. With 20-hr reaction times, all of the platinum complexes showed similar extents of reaction with DNA and caused approx equal losses of transforming activity. The stereoisomeric form of the diaminocyclohexane ligand of the DDCP or SHP complexes did not affect either the reactivity of the complex with DNA or its ab ility to reduce the trans-

forming activity of DNA. Significant increases in the number of lung adenomas in A/J mice were induced by multiple ip injections of cis-DDP and each of the DDCP and SHP complexes (total doses, 21 to 108 umol/kg body wt). Similar treatments with cis-DDP caused a significant increase in the number of skin papillomas in female CD-1 mice given promoting treatments with croton oil; the DDCP and SHP complexes had little or no activity in this system. At these levels, trans-DDP was not active for the induction of either lung adenomas or skin tumors. With the systems used for this study, the mutagenicities and tumorigenicities of the platinum(II) complexes did not correlate with their reported antitumor activities. Further studies appear warranted to determine whether there may be effective antitumor platinum (II) complexes that are not strongly mutagenic or carcinogenic. (Author abstract) (56 Refs)

8. STRUCTURAL BASIS OF THE MUTAGENICITY IN BACTERIA OF NITRATED NAPHTHALENE AND DERIVATIVES.

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Environ Mutagen; 3(5):499-511 1981

The mutagenic activity of nitronaphthalenes and some of their derivatives was investigated in the Salmonella mutagenicity assay. The 2-nitro and 2-hydroxylaminonaphthalenes were more mutagenic than their corresponding 1-substituted analogs. The adducts induced by 1-nitronaphthalene differed chemically from those derived from the 2-nitro analog. For expression of the mutagenic action of these chemicals, reduction of the chemicals to the corresponding hydroxylamines was required. These differences in mutagenic responses may be due to the different DNA adducts that have been identified after reaction of hydroxylaminonaphthalenes with DNA. The nitroso-containing polycyclic chemicals might not derive their mutagenic activity from reduction to the corresponding hydroxylamines. If there is a relationship between mutagenicity in Salmonella and human risks, adjusting the conditions for combustion in engines such that extensive nitration is favored may decrease the emission of hazardous substances. On a molar basis, when a mutagen is capable of inducing frameshift mutations by adduct formation as well as by simple intercalation, then the activity induced by the adduct greatly exceeds the activity due to simple intercalators. While bicyclic 2-nitronaphthalene and 4-nitroquinoline-1-oxide and their metabolites are primarily base-substitution mutagens, the introduction of a third ring structure results in a different mutational mechanism leading to frameshift mutagens. (58 Refs)

9. THE THYMIDINE INCORPORATION INHIBITING SCREENING SYSTEM (TTS) TO TEST CARCINOGENIC SUBSTANCES (A NUCLEAR DNA SYNTHESIS SUPPRESSIVE SHORT TERM TEST).

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Arch Geschwulstforsch; 51(7):605-610 1981

A short-term screening test is described in which the effects of carcinogens on DNA synthesis were measured by the determination of the mean number of silver grains per nucleus in the renal tubule and liver epithelia of 14-day-old CBA mice following ip injection of carcinogen. Fifteen hr after the injection of 0.1 ml of the dissolved chemical in a concentration representing 15/30% of the LD50, 3H-thymidine was injected ip. Autoradiographs of the nuclei of the renal tubular epithelia and of the liver epithelium were examined by visual silver grain counting. From this test, it was demonstrated that carcinogenic compounds of several different chemical classes (nitrosated amines, azo dyes, azo compounds, aliphatic iso- and heterocycles, aromatic amines, and metallic ions) partially inhibited the nuclear incorporation of thymidine in a significant manner over a time period longer than 24 hr. This decrease was expressed as a decrease of the mean of the silver grain number per nucleus in comparison with unaltered controls. This decrease was used as a criterion for the suppressive effect of carcinogenic substances on the rate of nuclear DNA synthesis. No false-positive results were obtained for noncarcinogenic compounds. The effectiveness of this test is discussed. (6 Refs)

10. A POTENT MUTAGEN IN BROILED FISH. PART 1. 2-AMINO-3-METHYL-3H-IMIDAZO[4,5-F]QUINOLINE.

Kasai H, Yamaizumi Z, Nishimura S, Wakabayashi K, Nagao M, Sugimura T, Spingarn NE, Weisburger JH, Yokoyama S, Miyazawa T
Biology Div., Natl. Cancer Center Res. Inst., Chuo-ku, Tokyo, Japan
J Chem Soc [Perkin I]; (8):2290-2293 1981

Sun-dried sardines were broiled in normal fashion, ground, and extracted with methanol. The residue showed strong mutagenicity in Salmonella typhimurium strain TA98 in the presence of S-9 mixture, according to the Ames method. After further fractionation a neutral fraction was obtained that retained 40% of the mutagenicity of the original fraction. Purification yielded a mutagenic compound. The compound was identified by nuclear magnetic resonance spectrum and high- and low-resolution mass spectra as 2-amino-3-methyl-3H-imidazo[4,5-f]quinoline (AMIQ). The identification was confirmed by synthesis of the compound. The structure is a six-six-five-membered ring. The mutagenicity of AMIQ was much higher than that of other mutagens isolated from protein pyrolysis products. The cause of the high mutagenicity is as yet unknown. (32 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN VERTEBRATES

11. THE INCORPORATION OF 5-FLUORO-2'-DEOXYURIDINE INTO DNA OF MAMMALIAN TUMOR CELLS.

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Dept. Biochemistry, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Biochem Biophys Res Commun; 102(2):654-658 1981

The mechanism of cytotoxicity of 5-fluoro-2'-deoxyuridine (FdUrd) in L1210 mouse leukemia cells was studied in vitro. L1210 cells were incubated with 10(-6) M [3H]FdUrd for 4 hr. DNA was then isolated and hydrolyzed. DNA content of [3H]FdUrd was measured by forming complexes with excess thymidylate synthetase in the presence of 0.1 milliM 5,10-methylenetetrahydrofolate. Treatment resulted in binding of 87% of total radioactivity to protein, indicating that most of the radioactivity was present as 5-fluoro-2'-deoxyuridylic acid (FdUMP). The incorporation of FdUrd amounted to 6.1 x 10(-9) moles of FdUMP/mole of DNA phosphate or 1 molecule of FdUMP/1.6 x 10(8) nucleotides. This level of incorporation was insufficient to account for previously reported mutagenesis by fluorinated pyrimidines. Apparently incorporation of 5-

fluorouracil into DNA does not play a significant role in the cytotoxicity of FdUrd in L1210 cells. (21 Refs)

12. POSTRADIATION DNA REPAIR IN MAMMALIAN CELLS AFTER COMBINED EXPOSURE TO HYPERTHERMIA, 8-BROMOCAFFEINE, AND ACTINOMYCIN D.

Rezvaia SP, Khanson KP
Central Res. Roentgenoradiological Inst., Leningrad, USSR
Radiobiologiia; 21(3):326-329 1981

The effect of combined exposure to hyperthermia, 8-bromocaffeine (BC), and actinomycin D (AD) on DNA repair was studied in irradiated (5,000 rads) LL cells. The level of double-stranded DNA after incubation with BC or AD at 41 C was significantly greater than that at 37 C. These findings indicate that hyperthermia does not enhance the inhibitory effect of BC and AD. (14 Refs) (In RUS)

13. ON THE IMMUNOLOGICAL DETECTION OF X-RAY INDUCED DNA DAMAGE.

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Radiat Environ Biophys; 19(4):259-264 1981

The possibilities of an immunological assay for the detection of x-ray induced DNA damage were examined. Three methods were used to investigate the binding between x-irradiated DNA and antisera obtained from immunized rabbits: modified Farr-test, micro-complement binding reaction, and isopycnic ultracentrifugation in a CsCl-gradient. In the Farr-assay, a rather high binding to unirradiated DNA and only a small increase with radiation was observed. The increase with dose was very small and hardly significant. The micro-complement test gave similar findings. A clear equivalent region could be found for x-irradiated as well as for unirradiated calf thymus DNA. If excess unirradiated DNA was added, however, no equivalence region was discovered which demonstrated that binding was nonspecific. With isopycnic centrifugation, there appeared to be a specific binding since 3H-labeled x-irradiated DNA was in found in the protein-DNA band. However, excess unirradiated calf thymus DNA caused this peak to shift to the DNA band. Binding could also be found with unirradiated 3H-DNA. When graded amounts of unirradiated unlabeled DNA were added to the samples with irradiated 3H-DNA, the peak height was progressively reduced. The results indicated that x-irradiated DNA is only a very weak specific antigenic determinant, if at all, and therefore, that immunological methods are not applicable as they are in the investigation of of x-ray-induced damage in biological systems after UV-exposure. (14 Refs)

14. EARLY POSTRADIATION CHANGES IN CHROMATIN FROM RAT THYMUS: MG++ LEVEL AND INTENSITY OF DEGRADATION AFTER EXPOSURE TO ENDONUCLEASES.

Chirkova LP, Ermolaeva NV
No affiliation given
Radiobiologiia; 21(3):335-340 1981

The changes in the Mg++ content and the rate of chromatin degradation were studied in random-bred and Wistar rats irradiated with 600 R. Animals were sacrificed 0.5, 1, and 2 hr after irradiation, and chromatin specimens isolated from the thymus were subjected to spectrofluorometry. There was a 65-90% increase in the Mg++ content and a 2-3-fold increase in the rate of endonuclease-induced chromatin degradation at pH of 6.4-6.5. (16 Refs) (In RUS)

15. ARE INDUCIBLE COMPONENTS INVOLVED IN THE REPAIR OF IRRADIATED NEURONAL AND BRAIN TUMOUR DNA?

Wheeler KT, Wierowski JV, Ritter P
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Int J Radiat Biol; 40(3):293-296 1981

Repair of irradiated neuronal and brain tumor DNA was studied in male Fisher 344 rats bearing 100-200 mg intracerebral 9L brain tumors irradiated with doses of 12.5 or 25.0 Grays (Gy) of Cesium-137 gamma rays at a dose rate of 9.21 Gy/min. After single doses of either 12.5 or 25.0 Gy, the restoration of chromosomal DNA structure in cerebellar neurons was slower than that in intracerebral tumor cells. DNA repair kinetics after a second dose of 12.5 or 25.0 Gy were identical to those obtained after single dose for both tumor cells and cerebellar neurons. Mean of all values on the plateau region of each curve after a single dose was not statistically different from the mean of values obtained after fractionated doses. Results indicated that the slower DNA repair in permanently nondividing neurons is a fundamental property of these cells and not an artifact of the high dose used initially. Evidence did not suggest that the slower repair results from the need to induce a specific component of the repair system. Consequently, difference in quality, quantity, or type of repair enzymes or difference in accessibility of these enzymes to or interference with their operation at the lesions are more attractive hypotheses to explain the slower DNA repair in neurons as compared with brain tumor cells. (5 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN INVERTEBRATES AND LOWER EUKARYOTES

16. COMPARISON OF SENSITIVITY OF RAD MUTANTS OF DIPLOID YEAST TO HEAT AND GAMMA RADIATION: CELLULAR TARGET FOR HEAT INACTIVATION.

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Div. Radiological Protection, Bhabdha Atomic Res. Centre, Trombay, Bombay-400 085, India
Int J Radiat Biol; 40(3):235-243 1981

Wild type and radiation-sensitive mutants rad 53, 54 and 55 of the diploid yeast Saccharomyces cerevisiae, in stationary and log phase were exposed to gamma radiation and hyperthermia (51 C) in order to compare their sensitivity to these agents. The wild type diploid strain exposed to gamma rays showed a sigmoidal survival curve both in stationary and log phase cultures. Log phase cells were significantly more resistant than stationary phase cells. When compared to wild type, the gamma radiation response of the mutants indicated that the mutations in these RAD loci render the cells sensitive in stationary phase and very sensitive in log phase. The response of mutants to hyperthermia was similar to that of wild type cells in both the phases. The log phase cells of both wild type and mutants were more sensitive to heat than stationary phase cells. These results suggest that the RAD loci are not involved in

the repair of hyperthermic damage. Since it is known that the products of the RAD genes are involved in the repair of DNA damage, the wild type response of these rad mutants to hyperthermia indicates that the DNA may not be the principal target for hyperthermic killing. Furthermore, the enhanced thermal sensitivity of log phase cells, containing higher amounts of active enzymes and sensitive membrane, strongly suggests that proteins and/or membranes could be the primary targets for thermal inactivation. (Author abstract) (29 Refs)

17. ASSESSING CONSEQUENCES OF MARINE POLLUTION BY HYDROCARBONS USING SPONGES AS MODEL ORGANISMS.

Zahn RK, Zahn G, Muller WE, Kurelec B, Rijavec M, Batel R, Given R
Physiologisch-Chemisches Institut, Universat Mainz, D-6500 Mainz, W. Germany
Sci Total Environ; 20(2):147-169 1981

Mutagenic activity in marine sponges (mainly Tethya lyncurium from the Northern Adriatic and from Catalina Island off Los Angeles, California) due to polycyclic aromatic hydrocarbon (PAH) pollution was investigated using radiolabeled benzo(a)pyrene (BaP) as a model pollutant. Tethya was exposed to Diesel 2 oil pollution at a level of 1-6 ppm. The amount of label converted into any one of three polyamines changed significantly: in controls, 30% ornithine decarboxylated were found as amines, while under conditions of oil pollution 80% were found as amines. With the Ames test the pollutant level was shown to be 3+ (equivalent to 0.7 ppb BaP). Ornithine decarboxylase activity increased slightly during the first 16 days of exposure, but had increased 10x by day 24. An increase in DNA-dependent RNA polymerase activity was seen with exposure to 1 ppm Diesel 2 for 1-2 days; the increase was only significant 1-2 days after exposure. Mixed function oxidase (MFO) activity could not be detected. Significant coupling of BaP derivatives to protein, DNA, and RNA was observed; the largest amount disappeared in the protein fraction. When illumination of 5 x 10(4) lux was omitted, the coupling of BaP derivatives to the DNA fraction dropped to 1/74x the previous values or less. Increased binding of BaP derivatives to DNA in the presence of light was significant between 0.001 and 31 ppb. However, when activated microsomal fractions from fish that had been exposed to high levels of PAH were added, dark incorporation rose to significant levels which could be decreased by the addition of the MFO inhibitor 7,8-benzoflavone. Possible absence of DNA repair in the sponges is discussed. (52 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN BACTERIA

18. BLOCKING BY THE CARCINOGEN, L-ETHIONINE, OF SOS FUNCTIONS IN A TIF-1 MUTANT OF ESCHERICHIA COLI B/R.

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Cancer Res; 41(11,part1):4382-4385 1981

In Escherichia coli, DNA damage by carcinogenic agents results in the coordinate expression of a diversity of functions (SOS functions), many of which are thermally inducible without any damage to DNA in a tif-1 mutant. These include prophage induction, filamentous growth, and an error-prone DNA repair activity, which is responsible for UV-induced mutagenesis. Ethionine causes hepatic carcinoma in rats after prolonged feeding but is not a mutagen in the Ames test. The present study shows that 10 mM ethionine prevents the thermal induction of lambda-prophage in a tif-1 derivative of E. coli. The enhancement of mutation, which normally occurs at high temperature after a low dose of UV light, is also blocked by ethionine. Ethionine does not block, to any appreciable extent, the incorporation of radioactive precursors into RNA, DNA, or protein. (Author abstract) (30 Refs)

19. USE OF EXONUCLEASE III TO DETERMINE THE SITE OF STABLE LESIONS IN DEFINED SEQUENCES OF DNA: THE CYCLOBUTANE PYRIMIDINE DIMER AND CIS AND TRANS DICHLORODIAMMINE PLATINUM II EXAMPLES.

Royer-Pokora B, Gordon LK, Haseltine WA
Dept. Pathology, Sidney Farber Cancer Inst., Harvard Medical Sch., 44 Binney St., Boston, MA, 02115
Nucleic Acids Res; 9(18):4595-4609 1981

A method to detect chemically stable lesions in DNA has been developed using Exonuclease III, a double strand specific nuclease, to digest 5'-end labeled DNA. The products, when analyzed on high resolution DNA sequencing gels, reveal the sites of DNA modification. Cyclobutane pyrimidine di mers induced by UV irradiation can be localized by comparison of the fragments produced by Exonuclease III digestion with fragments obtained after digestion of the DNA with UV specific endonuclease. The experiments demonstrate that Exonuclease III stops one base away from the cyclobutane pyrimidine dimers. Similar experiments with cis- and trans-dichlorodiammine-platinum (II) showed that modifications of DNA by these agents also impede Exonuclease III digestion. In general the same stop sites were found for cis- and trans-platinum adducts. They occur at sites of adjacent guanine bases. Additional stop sites were found for cis-platinum at sites of adjacent guanine bases. These results are in agreement with the model that cis-platinum forms intrastrand guanine-guanine dimers, whereas trans-platinum does not. (Author abstract) (31 Refs)

20. LETHAL EFFECTS OF NATURAL SOLAR ULTRAVIOLET RADIATION IN REPAIR PROFICIENT AND REPAIR DEFICIENT STRAINS OF ESCHERICHIA COLI: ACTIONS AND INTERACTIONS.

Tyrrell RM, Souza-Neto A
Dept. Carcinogenesis, Swiss Inst. for Experimental Cancer Res., 1066, Epalinges, Switzerland
Photochem Photobiol; 34(3):331-337 1981

The inactivation of repair proficient (Escherichia coli K12 AB 1157, E coli B/r) and repair deficient (E coli K12 AB 1886 uvrA, AB 2463 recA and AB 2480 uvrA recA) strains of bacteria by noon sunlight has been measured. The use of biological dosimetry based on an UV sensitive strain of Bacillus subtilis spores has allowed a quantitative comparison of bacterial inactivation by solar, 254 and 302 nm radiations. Our analysis indicates that: (1) uvrA and recA gene products are involved in repair of a substantial portion of the solar DNA damage, (2) 302 nm is a more appropriate wavelength than 254 nm to represent the DNA-damaging action of sunlight and that (3) repair proficient strains are inactivated by sunlight more rapidly than expected from the levels of DNA damage induced. When populations of repair proficient bacteria are exposed to noon sunlight for 20 min, they become sensitive to the lethal action of

far-UV (254 nm), MMS (0.1 M) and to a lesser extent, mild heat (52 C). (Author abstract) (18 Refs)

MACROMOLECULAR BINDING OF CARCINOGENS

21. NEOCARZINOSTATIN CHROMOPHORE: PURIFICATION OF THE MAJOR ACTIVE FORM AND CHARACTERIZATION OF ITS SPECTRAL AND BIOLOGICAL PROPERTIES.

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Dept. Pharmacology, Harvard Medical Sch., Boston, MA, 02115
Biochemistry; 20(19):5602-5608 1981

The nonprotein chromophore of neocarzinostatin (NCS-Chrom) can be separated by high-performance liquid chromatography into two components, A and B, with 90% and 10%, respectively, of the total UV-absorption. Each component possesses in vitro DNA scission activity equal to NCS, as does a third component, C, which is present only when NCS is extracted with nonacidic methanol and appears to be derived from A. NCS-Chrom A possesses in vivo activity equal to NCS; B and C have about 5% and 80%, respectively, of the activity of NCS for inhibition of HeLa cell growth. NCS-Chrom A possesses characteristic absorption, fluorescence, circular dichroism (CD), and magnetic circular dichroism (MCD) spectra. The spectral properties of B and C are similar to those of A. NCS-Chrom D can be generated by hydrolysis of each of the three active components at pH 8. It possesses a very different CD spectrum and, in contrast to NCS-Chrom, possesses no MCD, indicating a major change in or loss of the naphthoic acid residue. NCS-Chrom D is the 490-nm fluorescent product generated when NCS-Chrom spontaneously looses biological activity in aqueous pH 8 buffers. The optical activity of the biologically active NCS-Chrom accounts for the Cotton effects previously observed for native NCS. Changes in both the absorption and CD spectra of NCS-Chrom A (and B and C) occur on binding to apo-NCS, generating spectra identical with those of native NCS and providing stoichiometry of the association process. Complex formation between NCS-Chrom and DNA is also detected by CD, with the max effect being observed at low molar ratios of NCS-Chrom to DNA. Hypochromicity between 290 and 330 nm and a bathochromic shift centered near 365 nm occur upon binding of NCS-Chrom to apo-NCS and to DNA. (26 Refs)

22. METAL MUTAGENS AND CARCINOGENS EFFECTIVELY DISPLACE ACRIDINE ORANGE FROM DNA AS MEASURED BY FLUORESCENCE POLARIZATION.

Richardson CL, Verna J, Schulman GE, Shipp K, Grant AD
Meloy Laboratories, Inc., 6715 Electronic Drive, Springfield, VA, 22151
Environ Mutagen; 3(5):545-553 1981

Investigations were conducted to determine if DNA interactions with nonintercalative agents could be measured in the acridine orange displacement assay, to study the relative DNA reactivity of carcinogenic and noncarcinogenic metals in this system, and to determine if a correlation between DNA binding and mutagenic or carcinogenic effects could be established. Initial studies with cis-dichlorodiammineplatinum (II) (cis-Pt) demonstrated that acridine orange displacement from DNA, as measured by fluorescence polarization, was a direct result of cis-Pt-DNA binding. When the assay was applied to 13 additional metals, a concentration-dependent inhibition of acridine orange-DNA binding was noted. The shapes of the dose-response curves were generally sigmoidal. The interactions of the 13 metals with DNA were observed within 2 min and remained constant over 2 hr, in contrast with cis-Pt interaction which was optimal at 20 hr. Sodium, potassium, and lithium salts required the highest concentration for activity to displace acridine orange, the activities for the carcinogenic/mutagenic metals were substantially lower, and t he activities of magnesium and calcium were intermediate. Thus, this assay provides a relative measure of the interaction of metals with DNA, and this DNA reactivity shows a positive correlation with the mutagenic/carcinogenic potential. (35 Refs)

23. QUANTUM CHEMICAL STUDIES OF METHYL AND FLUORO ANALOGS OF CHRYSENE: METABOLIC ACTIVATION AND CORRELATION WITH CARCINOGENIC ACTIVITY.

Poulsen MT, Loew GH
(c/o Loew) Life Sciences Div., SRI International, 333 Ravenswood Ave., Menlo Park, CA, 94025
Cancer Biochem Biophys; 5(2):81-90 1981

Specific electronic properties related to metabolic transformation and adduct formation by DNA were calculated for a series of methyl, dimethyl and n-fluoro-5-methyl derivatives of chrysene with the aim of identifying molecular properties which could be used as reliable indicators of their relative carcinogenic behavior. Using the semiempirical all valence electron IEHT method, the bay region bonds of 5MC were found to have enhanced nucleophilic reactivity to epoxide formation relative to chrysene. In addition, in one of the nonequivalent bay regions, the 1, 2, 3, 4 region, the distal (1, 2) bond was found to be more reactive than the proximal (3, 4) bond. This reactivity pattern leads to an easily formed diol epoxide carbocation, the postulated ultimate carcinogen. By contrast, in the other (7, 8, 9, 10) bay region, the proximal (9, 10) bond is the more reactive, suggesting formation of the 'wrong,' ie, less stable diol epoxide carbocation. Consistent with earlier studies of other PAH, calculations by the INDO method of the ease of carbocation formation from a bay region diol epoxide yielded a set of values which gave a good correlation with carcinogenicity. (Author abstract) (29 Refs)

24. INHIBITION IN VIVO OF THE FORMATION OF ADDUCTS BETWEEN METABOLITES OF BENZO(A)PYRENE AND DNA BY BUTYLATED HYDROXYANISOLE.

Anderson MW, Boroujerdi M, Wilson AE
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709
Cancer Res; 41(11,part1):4309-4315 1981

Antioxidants have been shown to inhibit the carcinogenic effects of a variety of chemical carcinogens. For example, the phenolic antioxidant butylated hydroxyanisole (BHA) has been shown to be a potent inhibitor of benzo(a)pyrene (BP)-induced neoplasia in mouse lung and forestomach. The objective of the present study was to determine whether or not BHA, under conditions known to result in inhibition of BP-induced neoplasia, affects the formation of BP metabolite:DNA adducts. Following po administration of a carcinogenic dose of [3H]BP to A/HeJ mice, radioactivity was detected in the DNA of both lung and liver. Analysis of the deoxyribonucleosides by high-pressure liquid chromatography showed that the major adduct

in both tissues cochromatographed with the (+-)-7beta, 8alpha-dihydroxy-9alpha,10alpha-epoxy-7, 8,9,10 tetrahydrobenzo(a)pyrene (BPDEI):deoxyguanosine adduct. The 7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene (BPDEI):deoxyguanosine adduct. The 7beta,8alpha-dihydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene (BPDEII):deoxyguanosine adduct was 10 to 15% of the BPDEI adduct in both lung and liver. Another adduct, possibly derived from BP phenol(s), was also detected in lung and was 10 to 20% of the BPDEI adduct. Treatment of animals with BHA decreased the amount of the BPDEI adduct in the lung and the liver approx 55 and 75%, respectively. The decrease in the amount of this adduct in the lung appears to correlate with the inhibition of pulmonary adenoma formation. Thus, BHA appears to inhibit BP-induced pulmonary adenoma formation by inhibiting the amount of the BPDE:DNA adducts formed in lung. Possible mechanisms by which BHA treatment inhibits the formation of BPDE:DNA adducts are discussed. (Author abstract) (44 Refs)

25. DOSE-DEPENDENCY OF 2-ACETYLAMINOFLUORENE BINDING TO LIVER DNA AND HEMOGLOBIN IN MICE AND RATS.

Pereira MA, Lin LH, Chang LW
Health Effects Res. Lab., US Environmental Protection Agency, Cincinnati, OH, 45268
Toxicol Appl Pharmacol; 60(3):472-478 1981

Binding of 2-acetylaminofluorene (2-AAF) to liver DNA and Hb in Sprague-Dawley rats and CD-1 mice of both sexes was determined to test proposals that Hb binding correlates with target organ DNA binding and carcinogenicity. In both species, 2-AAF binding to liver DNA and HB increased as a linear function of dose (1-100 umoles/kg, po). This indicated that the formation of reactive 2-AAF liver metabolites also was linearly related to dose. No sex difference was observed in 2-AAF macromolecular binding, except for an apparent higher liver DNA binding in female mice than in male mice. DNA binding was only 7x greater and Hb binding only 2.5x greater in rats than mice; thus the binding did not reflect the 246x greater carcinogenicity of 2-AAF in rat liver. The results indicated that Hb binding can be used to predict DNA binding and the systemic dose; however, the extent of DNA binding does not predict carcinogenic potency. (20 Refs)

26. ADDUCTS FROM THE REACTION OF O,O'-DIACETYL OR O-ACETYL DERIVATIVES OF THE CARCINOGEN 4-HYDROXYAMINOQUINOLINE 1-OXIDE WITH PURINE NUCLEOSIDES.

Bailleul B, Gallegue S, Loucheux-Lefebvre M-H
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Cancer Res; 41(11,part1):4559-4565 1981

The diacetyl derivative of 4-hydroxyaminoquinoline 1-oxide (4-HAQO), the proximate carcinogen of 4-nitroquinoline 1-oxide, was reacted in vitro with purine nucleosides to give five adducts (3 with guanosine and 2 with adenosine). The same nucleoside modifications were also obtained with a monoacetyl derivative of 4-HAQO which is probably 4-acetoxy-aminoquinoline 1-oxide. The structure of the major adduct (the so-called dG III) was identified as N-(deoxyguanosine-C8-yl)-4-aminoquinoline 1-oxide. The isolation of this adduct from the 4-HAQO-modified DNA in vivo provides strong support for the hypothesis that the acetyl derivatives of 4-HAQO constitute a good model for the ultimate carcinogen. (Author abstract) (21 Refs)

27. ROLES OF 2-HALOETHYLENE OXIDES AND 2-HALOACETALDEHYDES DERIVED FROM VINYL BROMIDE AND VINYL CHLORIDE IN IRREVERSIBLE BINDING TO PROTEIN AND DNA.

Guengerich FP, Mason PS, Stott WT, Fox TR, Watanabe PG
Dept. Biochemistry, Center Environmental Toxicology, Vanderbilt Univ. Sch. Medicine, Nashville, TN, 37232
Cancer Res; 41(11,part1):4391-4398 1981

The metabolism of [1,2-14C]vinyl bromide (VBR) to products irreversibly bound to DNA and protein was examined in rat liver microsomes, reconstituted cytochrome P-450 systems, and isolated hepatocytes. A role for cytochrome P-450 was confirmed using inhibition and reconstitution experiments. The major form of cytochrome P-450 involved in VBR metabolism does not appear to be either of the major isozymes induced by phenobarbital or beta-naphthoflavone, as determined by induction, reconstitution, and antibody inhibition studies. 2-Bromoethylene oxide and 2-bromoacetaldehyde, suspected metabolites of VBR, were synthesized and found to be substrates for rat liver epoxide hydrolase and equine liver alcohol dehydrogenase, respectively. These enzymes were used to probe the roles of the two possible metabolites in the irreversible binding of products of VBR to protein and DNA. Alcohol dehydrogenase was more effective than epoxide hydrolase in inhibiting the binding of VBR metabolites to protein in microsomal incubations. Epoxide hydrolase was effective in inhibiting the binding of VBR or vinyl chloride metabolites to calf thymus DNA added to such systems, but alcohol dehydrogenase was not. Similar results were obtained for binding of VBR metabolites to DNA in a reconstituted enzyme system. Reduced glutathione blocked nonenzymatic binding of 2-bromo[1,2-14C]acetaldehyde to protein but not DNA. Binding of vinyl chloride and VBR metabolites to protein was blocked by reduced glutathione, but binding to DNA was not. These results are consistent with the view that 2-haloethylene oxides are the major alkylating agents bound to DNA, and 2-haloacetaldehydes are the major alkylating agents bound to proein in these experimental systems. Studies with labeled 2-bromoacetaldehyde indicate that the slow kinetics of DNA binding by this compound is responsible in part for this phenomenon. Studies with isolated rat hepatocytes suggest that a significant portion of the total and reactive metabolites are able to leave these cells. In these systems, binding of metabolites of vinyl chloride to DNA outside the hepatocytes could be partially blocked by epoxide hydrolase or by alcohol dehydrogenase, implying that, as targets farther away from sources of reactive species are considered, the stabilities of these species become more important for reaction with nucleophilic sites. (Author abstract) (36 Refs)

EFFECT OF CARCINOGENS ON MACROMOLECULAR SYNTHESES

28. PLASMINOGEN ACTIVATOR: ANALYSIS OF ENZYME INDUCTION BY ULTRAVIOLET IRRADIATION MAPPING.

Miskin R, Reich E, Dixon K
Biochemistry Dept., Weizman Inst. Science, Rehovot, Israel
Mol Cell Biol; 1(10):884-890 1981

The UV sensitivity of plasminogen activator (PA) synthesis in normal and ts68 sarcoma virus-transformed chick embryo fi-

broblasts (CEF) was measured. The apparent size of the transcription units required for PA induction was examined using ribosomal RNA (rRNA) synthesis as a standard. PA induction by the tumor-promoting agent phorbol myristate acetate (PMA) in CEF was markedly inhibited at UV fluences greater than 300 ergs/square mm (mm2); at 500 ergs/mm2, intracellular PA was only slightly higher than in cultures receiving no PMA. When the PA levels in the irradiation PMA-treated cultures were corrected for unirradiated control levels, the reduction in PA induction was an exponential function of UV fluence. The value for the UV sensitivity of PA induction by PMA was converted to a target size of approx 6,600 base pairs. When PA values in transformed, PMA-treated cultures were corrected for base-line enzyme content of comparable cultures not exposed to PMA, an exponential decline was seen in PMA inducibility as a function of UV fluence. The results suggested that PA induction by PMA proceeds either by identical pathways in both transformed and normal CEF or at least by pathways that are indistinguishable on the basis of UV sensitivity. Although the level of the retinoate (RT) induction was appreciably lower than that produced by PMA and the precision of the enzyme assay reduced, RT induction was found to be significantly less UV-sensitive than that of PMA. An exponential decline in overall protein synthesis was observed as a function of UV fluence, but the slope showed that this process was much more UV resistant than either PMA- or RT-induced PA synthesis. Hence, any UV-induced damage to the cellular protein synthesizing equipment cannot account for the much larger fractional decrease seen with drug-stimulated PA induction. (30 Refs)

REVIEWS

29. ENZYMES INVOLVED IN THE REPAIR OF DAMAGED DNA.

Grossman L
Dept. Biochemistry, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 N. Wolfe St., Baltimore, MD, 21205
Arch Biochem Biophys; 211(2):511-522 1981

Enzymes responsible for the error-free repair of DNA damage induced by radiation and chemicals are reviewed. They include DNA glycosylases, photolyase, endonucleases, exonucleases, and DNA polymerases. Also discussed are repair due to metabolic alterations, mismatch base excision repair and reinsertion of nucleotides. (81 Refs)

30. ARE PYRIMIDINE DIMERS NON-INSTRUCTIVE LESIONS?

Lawrence CW
Dept. Radiation Biology and Biophysics, Univ. Rochester Medical Center, Rochester, NY, 14642
MGG; 182(3):511-513 1981

Published data from yeast and E coli show that base substitution induced by UV in pyrimidine-pyrimidine sequences is not random, and suggest that fidelity of DNA replication is not entirely lost during transdimer synthesis. These observations question whether cyclobutane pyrimidine dimers are truly non-instructive lesions. (Author abstract) (17 Refs)

31. EFFECT OF METALS ON MUTAGENESIS AND DNA REPAIR.

Rossman TG
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Environ Health Perspect; 40:189-195 1981

A review is presented of mechanisms of mutagenesis, effects on DNA repair leading to comutagenesis, and possible reasons why carcinogenic metals are not mutagenic in microbial systems. A classification of mutagenesis mechanisms is based on the possible modes of action of metals: misreplication due to altered DNA or decreased fidelity of DNA polymerase, inhibition of proofreading, and mutagenesis via error-prone DNA repair. Excision repair, mismatch repair, and two other alternative pathways (not involving cleavage of the phosphodiester bond and subsequent repair replication characteristic of excision repair) are discussed with respect to effects on DNA repair leading to comutagenesis. Bacteria have an inducible, error-prone DNA repair system (SOS repair) whose activity results in mutagenesis. In one of the best studied examples of metal mutagenesis, chromate, little evidence exists for involvement of the SOS system. Arsenite exemplifies metals that may act as comutagens by inhibiting repair of damage to DNA caused by another agent. Comutagens would not be detected by standard screening methods. (48 Refs)

32. METAL-INDUCED INFIDELITY OF DNA SYNTHESIS.

Zakour RA, Kunkel TA, Loeb LA
Joseph Gottstein Memorial Cancer Res. Lab., Dept. Pathol., Univ. Washington, Seattle, WA, 98195
Environ Health Perspect; 40:197-205 1981

Present state of knowledge, public health implications, and required research are reviewed. Topics discussed include mechanism of DNA polymerization, fidelity of DNA synthesis, assays with polynucleotide templates, metal activators and non-activating metal ions and fidelity, screening for metals that alter fidelity, fidelity of DNA synthesis with natural DNA templates, and mechanism of genetic miscoding by metals. A significant correlation exists between metals that decrease fidelity and those reported to be mutagenic and carcinogenic. To date greater than 40 metal compounds have been tested in graded concentrations for effects on fidelity of DNA synthesis. Compounds which increase infidelity by greater than 30% at two or more concentrations are scored positive: these included all the known mutagens/carcinogens (Ag, Be, Cd, Co, Cr, Mn, Ni, Pb), although evidence in the literature is equivocal for three metals. Of these, Cu++ increased misincorporation and Fe++ and Zn++ did not alter fidelity. With few exceptions these results have been confirmed. The general postulate that carcinogens can be identified by their interactions with DNA includes metals. (37 Refs)

33. RECENT RESEARCH ON NICKEL CARCINOGENESIS.

Sunderman FW
Dept. Lab. Medicine, Univ. Connecticut Sch. Medicine, Farmington, CT, 06032
Environ Health Perspect; 40:131-141 1981

Nickel carcinogenesis research since 1975 is reviewed, with emphasis on new experimental techniques for studying carcinogenesis in vivo and in vitro. The subjects covered include epidemiologic studies, clinical investigations, carcinogenicity tests in animals exposed to nickel compounds by different administration routes, x-ray diffractometry and radiotracer studies of alpha-Ni3S2 metabolism, electron microscope studies of alpha-

Ni3S2-induced tumors, cytogenetic and tumor transplantation studies, effects of nickel compounds on DNA synthesis, cell culture studies, bacterial mutagenicity tests, and effects of metals on viral and bacterial DNA polymerase. Prospects for future research on nickel carcinogenesis are summarized. (82 Refs)

34. ROLE OF COBALT, IRON, LEAD, MANGANESE, MERCURY, PLATINUM, SELENIUM, AND TITANIUM IN CARCINOGENESIS.

Kazantzis G

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Environ Health Perspect; 40:143-161 1981

Experimental, clinical, and epidemiological studies of the carcinogenicity of cobalt, iron, lead, manganese, mercury, platinum, selenium, and titanium are reviewed. Sources of exposure to these metals and their mutagenic effects are discussed. Excess lung cancer mortality has been observed in hematite miners, but occupational exposure to the other metals is not associated with an increased cancer risk. Platinum coordination complexes used in cancer chemotherapy are electrophilic reactants and thus capable of cancer initiation. Cobalt oxide and cobalt sulfate produce injection site and renal tumors in animals, and both are mutagenic. Manganous acetylacetonate and dichlorodicyclopentadienyl titanium also give rise to injection site tumors, but only the latter is mutagenic. Mercury compounds do not appear to be carcinogenic, although some produce genetic damage. The mutagenicity and carcinogenicity of selenium have not been established. (142 Refs)

35. THE ROLE OF METALS IN CARCINOGENESIS: BIOCHEMISTRY AND METABOLISM.

Jennette KW

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Environ Health Perspect; 40:233-252 1981

A review is presented of the biochemistry and metabolism of inorganic species involved in carcinogenesis. Such species may have a role in transport across the cell membrane, enzymatic and chemical transformation of redox active inorganic species within the cell, coordination to cellular small molecules and macromolecules, and inhibition, activation or change of specificity of cellular enzymes by inorganic species. Oxide complexes are discussed with respect to enzyme interaction, metabolism, and mutagenicity. The role of divalent ions is examined. Oxyanions of V, Cr, Mo, As, and Se cross cell membranes; once inside the cell they may act as phosphate and/or sulfate analogs, inhibiting enzymes which catalyze phosphoryl or sulfuryl transfer reactions. They may serve as alternate enzyme substrates, but they form ester products which are hydrolytically unstable and decompose readily in aqueous soln. The divalent ions of Be, Mn, Co, Ni, Cd, Hg, and Pb are stable forms which may mimic essential divalent ions such as Mg, Ca, Fe, Cu, or Zn. These ions may complex small molecules, enzymes, and nucleic acids so as to alter the normal activity of these species. Free radicals produced in the presence of these metal ions may damage critical cellular molecules. (216 Refs)

36. RELATIONSHIP BETWEEN METAL TOXICITY TO SUBCELLULAR SYSTEMS AND THE CARCINOGENIC RESPONSE.

Squibb KS, Fowler BA

Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709

Environ Health Perspect; 40:181-188 1981

Subcellular systems that influence ultimate cellular responses to toxic and carcinogenic metals are reviewed. They include the endoplasmic reticulum (microsomal enzyme systems and protein synthesis), nuclei, mitochondria, lysosomes, and cellular membranes. Cell membranes regulate carcinogen uptake; microsomal enzymes are responsible for carcinogen metabolism; mitochondria and lysosomes can affect detoxification and storage of carcinogens; and nuclear DNA polymerases can repair carcinogen-induced damage. (102 Refs)

37. CHELATING AGENTS IN BIOLOGICAL SYSTEMS.

Schubert J

Dept. Chemistry, Univ. Maryland Baltimore County, Catonsville, MD, 21228

Environ Health Perspect; 40:227-232 1981

A review is presented of selected aspects of the chemistry of metal ions, chelate formation, and stability of metal chelates. Subjects discussed include chelate formation and in vivo stability (including rate effects), mixed (ternary) complexes, oxidation-reduction, and biological consequences and applications (including lipophilicity and intracellular transport, catalase-like activity, and viral interactions). Complexes and chelates of platinum(II) such as cis-dichlorodiammineplatinum are useful in canc er chemotherapy. Other active Pt complexes include those in which one ligand is bidentate, such as dichloroethylenediammineplatinum. These Pt compounds could conceivably interact with DNA via ternary complex formation. The ability to use mixed complex formation as a ligand scavenger for transporting ligands makes possible utilization of nontoxic binary chelates for the transport of chemotherapeutic drugs to target sites. Metal and ligand scavenging play a role in the induction or reversal of mutagenic effects. The so-called role of metals in carcinogenesis could reflect transport of binary and ternary complexes of the metals to and from intracellular target sites. (32 Refs)

38. EFFECTS OF METALS IN IN VITRO BIOASSAYS.

Sirover MA

Dept. Pharmacology, Temple Univ. Sch. Medicine, Philadelphia, PA, 19140

Environ Health Perspect; 40:163-172 1981

In vitro bioassays for detecting the mutagenicity and potential carcinogenicity of metal compounds are reviewed. Assays discussed include the Salmonella typhimurium and Escherichia coli assays that quantitate the ability of metals to revert the bacteria to histidine prototrophy and to tryptophan prototrophy, respectively, and the use of Bacillus subtilis strains deficient in DNA repair to determine growth inhibitory effects of metals. Other bioassays examine the ability of metals to induce thioguanine or azaguanine resistance in Chinese hamster cells, enhance viral transformation in hamster cells, transform Syrian hamster cells, and induce chromosome aberrations in hamster and rat cells and human lymphocytes. Correlations between in vitro bioassays and in vivo carcinogenicity are discussed. (82 Refs)

39. ACTIVATED METABOLITES OF CARCINOGENIC HYDROCARBONS.

Harvey RG
Ben May Lab., Univ. Chicago, Chicago, IL, 60637
Acc Chem Res; 14(7):218-226 1981

Elucidation of the structures of active polycyclic aromatic hydrocarbon metabolites and of the pathways leading to their formation are reviewed with respect to implications for the mechanism of cancer induction. Major topics discussed include metabolism, K-region arene oxides, diol epoxide metabolites of other polyarenes, diol epoxide-nucleic acid interaction, and theories of carcinogenesis. Although much is now known in the areas of metabolic activation and tumor initiation, unanswered questions remain concerning the relation of DNA alkylation and tumor induction, regioselectivity of alkylation, fidelity of transcription, and nucleic acid repair and errors during repair. (123 Refs)

40. SISTER CHROMATID EXCHANGE (SCE) AND STRUCTURAL CHROMOSOME ABERRATION IN MUTAGENICITY TESTING.

Gebhart E
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Hum Genet; 58(3):235-254 1981

An objective analysis is presented of data gained so far relative to the value i n mutagenicity testing of sister chromatid exchange (SCE) and classical chromosome aberration (CA) analysis. Detailed studies are reported on spontaneous SCE and chromosome damage in normal cells, and in cells of patients with genetic and neoplastic disease. Qualitative results on SCE induction and CA are presented relative to radiation, chemicals, chromosomal breakage syndromes and virus. Quantitative results are presented on potent inducers of SCE and break aberrations, substances inducing SCE but not breaks in the same test system, and clastogens with no or minor SCE-inducing activity. A section deals with modification of SCE and chromosome breakage: clastogens and anticlastogens. A discussion of molecular aspects of SCE induction and breakage involves consideration of evidence for the primary lesions leading to SCE formation, role of replication and involvement of repair mechanisms. These studies indicate SCE and structural CA are two largely different cytogenetic endpoints of mutagenic action. It is suggested that the SCE-technique is a valuable additional method for cytogenetic testing, which, however, is not adequate to replace the classical methods of analysis of structural chromosome damage. (165 Refs)

41. SISTER CHROMATID EXCHANGES: A REPORT OF THE GENE-TOX PROGRAM.

Latt SA, Allen J, Bloom SE, Carrano A, Falke E, Kram D, Schneider E, Schreck R, Tice R, Whitfield B, Wolff S
Harvard Medical Sch., Boston, MA, 02115
Mutat Res; 87(1):17-62 1981

Sister chromatid exchange (SCE) as a test for mutagenic carcinogens is reviewed. Method of testing is described with respect to the genetic basis for SCE, and to cell types and animal strains for in vitro and in vivo studies. Interpretation of data is explained, including presentation (dose-response curves, data transformation, and units of expression), statistical evaluation, and criteria for negative/positive conclusions (negative agents, positive agents, provisionally positive agents). Test performance is reviewed with citations of literature, chemicals or chemical classes that give anomalous results (deoxycytidine, ascorbate, and methotrexate), chemicals or chemical classes for which the test is well suited (alkylating agents, many DNA-binding agents, certain DNA-base analogues, and agents that cause single-strand breaks), and correlation with mammalian carcinogenicity data. A protocol is suggested using in vitro and in vivo SCE analysis, and non-mammalian systems for detecting mutagens using the SCE procedure. Conclusions on the strengths and weaknesses of the assay, its role in a testing program, and recommendations for future research are presented. (169 Refs)

42. MECHANISMS OF MALIGNANT GROWTH.

Grundmann E
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Klin Wochenschr; 59(17):931-941 1981

Analysis of invasive malignancy focuses on the particularly high growth rate of tumor cells, and on the aggressive mechanisms of histolysis favoring the infiltration of the malignant cells into the surrounding tissue. Specific significance is attributed to a certain enzyme directed against Type IV collagen, and to the auto-locomotion of tumor cells, properties that may also explain the highest selective process of metastasization in at least three consecutive steps: Tumor cells invade a blood or lymph vessel, they are transported along blood or lymphatic pathways, and they eventually infiltrate foreign tissue after penetration and destruction of blood or lymph vessel walls. Among the factors involved in the process of metastasization, special interest is due to blood coagulation and to the coexistence of different tumor cell subpopulations within a primary. These features of malignant growth are based on the loss of functional differentiation as manifested eg in the loss of tissue-specific nuclear chromatin structures. Tumor development is triggered by the so-called primary factors which always affect the DNA, ie, the cell genome. Chemical carcinogens, viruses, and shortwave or ionizing irradiation induce DNA defects which, however, will be reversed and mended by special repair mechanisms in most cases. Thus, the actual development and spread of malignancy is ultimately due to deficient reparation. Co-factors favoring and promoting carcinogenesis may shorten the latency period, among several other specific chemicals and hormones. Based on current knowledge of tumor dormancy a new concept is proposed for the chronological and morphological sequence of carcinogenesis: Following the development of a primary tumor, certain as yet undefined growth factors and especially immunological factors may be responsible for the development of a progressive tumor disease. (Author abstract) (62 Refs) (In GER)

43. SOMATIC MUTATION/NEODIFFERENTIATION/ SELECTION AND THE ORIGINS OF HUMAN CANCERS.

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Dept. Veterinary Science, Coll. Agriculture and Life Sciences, Univ. Wisconsin, 1655 Linden Drive, Madison, WI, 53706
Med Hypotheses; 7(9):1157-1168 1981

The etiology of cancer is considered in terms of underlying biological mechanisms: somatic mutation (an alteration in genomic information content) or defective differentiation (alteration in genomic information expression). Human carcinogens, including radiation, chemicals, and viruses or viral components, are discussed. Chemicals have been shown to be responsible for virtually all epithelial cancers. Considering human carcinogenesis to be a multistep procedure, it is possible to accept both hypotheses for the origin of cancer. According to the blocked ontogeny hypothesis of cancer, it is suggested that an

agent capable of blocking natural differentiation might bring about a partial or total blockage o f natural restraints on proliferation produced by differentiated cells. This theory is discussed in relation to hemoglobinopathies and thalassemias, caused by inherited mutations and genetic deletions that affect the development of Hb production. Others have suggested that most human cancers are not caused by local genomic mutation but are more likely the result of genetic transpositions or rearrangements. It is unknown whether or not or to what extent natural cellular differentiation is mediated by transpositions involving moveable genetic elements. The authors concluded that both genetic transposition and 'autocrine secretion' are within the confines of and consistent with the more general blocked ontogeny hypothesis, and together help provide a plausible mechanism for a somatic mutation/neodifferentiation/selection theory of human cancer. (51 Refs)

44. CARCINOGEN TESTING: CURRENT PROBLEMS AND NEW APPROACHES.

Weisburger JH, Williams GM
American Health Foundation, Valhalla, NY, 10595
Science; 214(4519):401-407 1981

The classic procedures for testing potential carcinogens in animals have basically not changed in the past 50 yr. Considerable knowledge of the mechanisms of carcinogenesis has accrued in the last 20 yr, particularly concepts on the metabolic activation of chemicals to reactive electrophilic compounds that can interact with nucleophilic cell components including DNA. These developments, in turn, have yielded a framework for integrating into carcinogen testing the determination of genetic effects of chemicals. A systematic decision point approach to carcinogen testing has been developed which entails a sequential decision-making process as specific tests are performed and evaluated prior to initiation of higher order, more complex tests. Compared to conventional bioassays in rodents, this approach provides knowledge based on mechanisms of carcinogenesis, yields a substantial amount of data at minimal cost, and forms a solid base for eventual health risk assessment. (Author abstract) (34 Refs)

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CHEMICAL CARCINOGENESIS

1. CHEMICAL COMPOUNDS AND CANCER RISK.

Schramm T, Janisch W
Zentralinstitut fur Krebsforschung der Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin, E. Germany
Arch Geschwulstforsch; 51(7):561-565 1981
In GER

2. THE CARCINOGENICITY OF ARSENIC.

Pershagen G
Dept. Environmental Hygeine, Karolinska Inst., Stockholm, Sweden
Environ Health Perspect; 40:93-100 1981

3. THE CARCINOGENICITY OF CHROMIUM.

Norseth T
Inst. Occupational Health, Gydas vei 8, Oslo 3, Norway
Environ Health Perspect; 40:121-130 1981

4. ROLE OF COBALT, IRON, LEAD, MANGANESE, MERCURY, PLATINUM, SELENIUM, AND TITANIUM IN CARCINOGENESIS.

Kazantzis G
TUC Centenary Inst. Occupational Health, London Sch. Hygiene and Tropical Medicine, Keppel St., London WC1E 7HT, England
Environ Health Perspect; 40:143-161 1981

5. RECENT RESEARCH ON NICKEL CARCINOGENESIS.

Sunderman FW
Dept. Lab. Medicine, Univ. Connecticut Sch. Medicine, Farmington, CT, 06032
Environ Health Perspect; 40:131-141 1981

6. ROLE OF CADMIUM IN CARCINOGENESIS WITH SPECIAL REFERENCE TO CANCER OF THE PROSTATE.

Piscator M
Dept. Environmental Hygiene, Karolinska Inst., S-104 01 Stockholm, Sweden
Environ Health Perspect; 40:107-120 1981

7. CHELATING AGENTS IN BIOLOGICAL SYSTEMS.

Schubert J
Dept. Chemistry, Univ. Maryland Baltimore County, Catonsville, MD, 21228
Environ Health Perspect; 40:227-232 1981

8. BENZENE AS A RISK FACTOR.

Stobbe H
Universitatsklinik fur Innere Medizin 'Theodor Brugsch', Bereich Medizin der Humboldt-Universitat, Schumannstrasse 20/21, DDR-1040 Berlin, E. Germany
Arch Geschwulstforsch; 51(7):575-578 1981
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9. FORMALDEHYDE IN DENTISTRY: A REVIEW OF MUTAGENIC AND CARCINOGENIC POTENTIAL.

Lewis BB, Chestner SB
800-A Fifth Ave., Suite 503, New York, NY, 10021
J Am Dent Assoc; 103(3):429-434 1981

10. CARCINOGENICITY OF HYDANTOINS: DATA, HYPOTHESES, AND PUBLIC REVIEWS.

Scoville B, White BG
Natl. Inst. Neurological and Communicative Disorders and Stroke, NIH, Bethesda, MD, 20205
Psychopharmacol Bull; 17(3):195-197 1981

11. PHENOXY ACIDS, CHLOROPHENOLS, AND CANCER.

Hardell L, Eriksson M
Onkologiska kliniken, Regionsjukhuset, Umea, Sweden
Lakartidningen; 78(34):2862-2863 1981
In SWE

12. PHENOXY ACIDS: A BRIEF REVIEW OF THE POSSIBLE HYGIENIC EFFECTS.

Edling C
Yrkesmedicinska kliniken, Regionsjukhuset, Linkoping, Sweden
Lakartidningen; 78(34):2861-2862 1981
In SWE

DIETARY FACTORS IN CARCINOGENESIS

13. NUTRITIONAL MODULATION OF CANCER.

Nauss KM, Newberne PM
Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139
Cancer Detect Prev; 3(2):367-417 1981

14. FIBER CARCINOGENESIS: EPIDEMIOLOGIC OBSERVATIONS AND THE STANTON HYPOTHESIS.

Harington JS
Cancer Res. Dept., Natl. Cancer Assoc. South Africa, P.O. Box 2000, Johannesburg 2000, South Africa
JNCI; 67(5):977-989 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

15. EPIDEMIOLOGY.

Alderson MR
Dept. Epidemiology, Inst. Cancer Res., London, England
Recent Results Cancer Res; 78:1-19 1981

16. ATLAS OF CANCER MORTALITY IN THE PEOPLE'S REPUBLIC OF CHINA. AN AID FOR CANCER CONTROL AND RESEARCH.

Li JY, Liu BQ, Li GY, Chen ZJ, Sun XD, Rong SD
Dept. Cancer Epidemiology, Cancer Inst. Chinese Acad. Medical Sciences, 2, Yabao Lu, Chaoyang, Qu, Beijing, People's Republic of China
Int J Epidemiol; 10(2):127-133 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

17. SIXTH EAST GERMAN CANCER CONGRESS WITH INTERNATIONAL PARTICIPATION, BERLIN, MARCH 2-5, 1981.

Schramm T, Ebeling K, Schwarz R, Heise E, Glaser A, Tanneberger St, Anger G
No affiliation given
Arch Geschwulstforsch; 51(7):551-560 1981
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18. EPIDEMIOLOGICAL STUDIES INTO THE POSSIBLE CARCINOGENICITY OF HAIR DYES.

Clemmesen J
(c/o P. Lohman), Medical Biological Lab. TNO., P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(1):65-79 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

19. THE ROLE OF METALS IN CARCINOGENESIS: BIOCHEMISTRY AND METABOLISM.

Jennette KW
Dept. Chemistry, Dartmouth Coll., Hanover, NH, 03755
Environ Health Perspect; 40:233-252 1981

20. RECENT CONCEPTS OF INITIATION AND PROMOTION IN CARCINOGENESIS.

Becker FF
M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Am J Pathol; 105(1):3-9 1981

21. ACTIVATED METABOLITES OF CARCINOGENIC HYDROCARBONS.

Harvey RG
Ben May Lab., Univ. Chicago, Chicago, IL, 60637
Acc Chem Res; 14(7):218-226 1981

22. RELATIONSHIP BETWEEN METAL TOXICITY TO SUBCELLULAR SYSTEMS AND THE CARCINOGENIC RESPONSE.

Squibb KS, Fowler BA
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709
Environ Health Perspect; 40:181-188 1981

23. ENZYMES INVOLVED IN THE REPAIR OF DAMAGED DNA.

Grossman L
Dept. Biochemistry, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 N. Wolfe St., Baltimore, MD, 21205
Arch Biochem Biophys; 211(2):511-522 1981

24. METAL-INDUCED INFIDELITY OF DNA SYNTHESIS.

Zakour RA, Kunkel TA, Loeb LA
Joseph Gottstein Memorial Cancer Res. Lab., Dept. Pathol., Univ. Washington, Seattle, WA, 98195
Environ Health Perspect; 40:197-205 1981

25. CHROMOSOME ABERRATIONS AND THEIR RELEVANCE TO METAL CARCINOGENESIS.

Vainio H, Sorsa M
Dept. Industrial Hygiene and Toxicology, Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Environ Health Perspect; 40:173-180 1981

MODIFICATION OF CARCINOGENESIS

26. METAL INTERACTIONS IN CARCINOGENESIS: ENHANCEMENT, INHIBITION.

Nordberg GF, Andersen O
Dept. Environmental Hygiene, Umea Univ., Umea, Sweden
Environ Health Perspect; 40:65-81 1981

27. EFFECT OF METALS ON MUTAGENESIS AND DNA REPAIR.

Rossman TG
Inst. Environmental Medicine, New York Univ. Sch. Medicine, 550 First Ave., New York, NY, 10016
Environ Health Perspect; 40:189-195 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

28. SISTER CHROMATID EXCHANGES: A REPORT OF THE GENE-TOX PROGRAM.

Latt SA, Allen J, Bloom SE, Carrano A, Falke E, Kram D, Schneider E, Schreck R, Tice R, Whitfield B, Wolff S
Harvard Medical Sch., Boston, MA, 02115
Mutat Res; 87(1):17-62 1981

29. EFFECTS OF METALS IN IN VITRO BIOASSAYS.

Sirover MA
Dept. Pharmacology, Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Environ Health Perspect; 40:163-172 1981

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BIOLOGICAL ASPECTS OF DNA ALTERATION AND REPAIR IN RELATION TO CARCINOGENICITY

1. KINETICS OF O6-METHYLGUANINE REPAIR IN HUMAN NORMAL AND ATAXIA TELANGIECTASIA CELL LINES AND CORRELATION OF REPAIR CAPACITY WITH CELLULAR SENSITIVITY TO METHYLATING AGENTS.

Shiloh Y, Becker Y
(c/o Becker) Dept. Molecular Virology, Hadassah-Hebrew Univ. Medical Sch., Post Office Box 1172, 91 010 Jerusalem, Israel
Cancer Res; 41(12):5114-5120 1981

Human lymphoblastoid cell lines from normal individuals and from patients with a taxia telangiectasia were either proficient or deficient in their ability to repair the mutagenic DNA adduct O6-methylguanine that is induced by methylating carcinogens. There was no relationship between the capacity to repair O6-methylguanine and the ataxia telangiectasia phenotype. Time-course studies done following a short pulse (2 min) of alkylation with 0.5 mg of N-[3H]methyl-N'-nitro-N-nitrosoguanidine per ml revealed that the repair of O6-methylguanine in human lymphoblastoid lines proficient in this ability is a rapid process, which proceeds with a half-life of 10 to 15 min. Lymphoblastoid lines with deficient capacity to repair this DNA adduct were hypersensitive to the cytotoxic effect of the methylating carcinogens N-methyl-N'-nitro-N-nitrosoguanidine, N-methyl-N-nitrosourea, and methyl methanesulfonate, and this hypersensitivity was correlated with the relative amount of O6-methylguanine induced by each of the three chemicals. This was taken as an indication of the lethality of unrepaired O6-methylguanine. The extent of DNA repair synthesis induced by the three carcinogens was the same in cell lines proficient and deficient in O6-methylguanine repair, indicating no major deficiency in an excision repair pathway in the hypersensitive cell lines. (Author abstract) (44 Refs)

2. INDUCTION AND REPAIR OF RADIATION DAMAGE IN DNA IN ATAXIA TELANGIECTASIA CELLS (MEETING ABSTRACT).

van Der Schans GP, Centen HB, Lohman PH
Medical Biological Laboratory TNO, P.O. Box 45, Rijswijk, The Netherlands
Int J Radiat Biol; 40(2):208 1981

Patients suffering from ataxia telangiectasia (AT), a hereditary disease, show an elevated radiosensitivity extending from the clinical to the cellular level. AT-cells have been claimed be deficient in repair of damage in DNA as judged from the decreased unscheduled DNA synthesis after irradiation with 60Co-gamma rays, in comparison to normal cells. We studied the repair of gamma ray induced single-strand breaks. After moderate to high doses (20-150 Gy), in normal cells a rapid and slow repair could be distinguished, representing two different types of lesions. Both types were also observed in irradiated AT3BI cells; repair was as in normal cells. After low doses in normal cells more than 50 per cent of the single-strand breaks were repaired within 2 min. For some cultures of AT-cells 3-6 min were needed for 50 per cent repair. Also double-strand breaks induced by 50 Gy of gamma rays were rapidly repaired, in normal as well as in four strains of AT-cells; within 10 min 50 per cent appeared to be rejoined, followed by a slower repair with a half-life of about 1 hr. In spite of the fact that the induction of double-strand breaks could be greatly reduced by irradiating in the absence of oxygen and in the presence of cysteamine, the repair pattern of normal and AT-cells did not change. Double-strand breaks, induced by the radiomi metic substance Bleomycin, were repaired only slowly. Here AT3BI and AT4BI cells differed from normal cells; after 2 hr of incubation more double-strand breaks remained. (no Refs)

3. COMPLEMENTATION ANALYSIS OF XERODERMA PIGMENTOSUM VARIANTS.

Jaspers NG, Jansen-van de Kuilen G, Bootsma D
Dept. Cell Biology and Genetics, Erasmus Univ. Rotterdam, 3000 DR Rotterdam, TheNetherlands
Exp Cell Res; 136(1):81-90 1981

DNA repair after UV exposure was studied in multinucleate cells, obtained after fusion of excision-defective and variant xeroderma pigmentosum fibroblasts. Optimal fusion conditions were determined, facilitating the measurement of DNA replication in heterokaryons. In unirradiated multikaryons, entry into the S phase was depressed, when compared with unfused cells. The extent of the depression of S phase entry was dependent on the fusion conditions. In heterokaryons obtained after fusion of XP variant (6 different strains) with excision-defective XP (3 cell strains from complementation groups A, C and D) both unscheduled DNA synthesis and post-replication repair after UV irradiation were restored to normal levels. In contrast, complementation was not observed after pairwise fusion of the XP variant cell strains. These results suggest that the XP variants comprise a single complementation group, different from complementation groups A, C and D. (Author abstract) (27 Refs)

4. INDUCTION OF PLASMINOGEN ACTIVATOR BY UV LIGHT IN NORMAL AND XERODERMA PIGMENTOSUM FIBROBLASTS.

Miskin R, Ben-Ishai R
Dept. Biochemistry, Weizmann Inst. Science, Rehovot, Israel
Proc Natl Acad Sci USA; 78(10):6236-6240 1981

Normal and DNA repair-deficient human fibroblasts have been used to study induction of plasminogen activator (PA) by DNA damage. UV light induced the synthesis of PA in skin fibroblasts of all types of xeroderma pigmentosum (XP) in XP heterozygotes and in human amniotic cells. Enzyme induction was, however, not observed in fibroblasts of normal adults. In classical XP, which are deficient in excision repair, PA synthesis occurred in a narrow range of low-UV fluences. In such strains, the level of enzyme produced was correlated with the extent of repair deficiency. UV fluences required for PA induction in XP variants and XP heterozygotes were at least 10x those inducing enzyme synthesis in excision-deficient XP. Max enzyme induction occurred 48 hr after irradiation, and the highest levels of enzyme produced were 15-20x those of PA baseline levels. Electrophoretic analysis showed that UV irradiation enhances the synthesis of the Mr 60,000 human urokinase-type PA, which is present in low amounts in untreated cells. Our results suggest that PA induction in human cells is caused by unrepaired DNA damage and represents a eukaryotic SOS-like function. In addition, PA induction may provide a sensitive assay for detection of cellular D NA repair deficiencies and identification of XP heterozygotes. (Author abstract) (42 Refs)

BIOLOGICAL ASPECTS OF DNA ALTERATION AND REPAIR IN RELATION TO MUTAGENICITY

5. SOME CARCINOGENIC, MUTAGENIC, AND BIOCHEMICAL PROPERTIES OF PLATINUM ANTITUMOR COORDINATION COMPLEXES AND OF S-VINYL- AND S-ETHYLHOMOCYSTEINE.

Leopold WR
The University of Wisconsin, Madison, WI
Diss Abstr Int [B]; 42(3):998-B 1981

It is known that cis-dichlorodiammineplatinum(II) (DDP), cis-dichlorobis(cyclopentylamine)platinum(II) (DCP), and the three stereoisomeric forms of dichloro-1,2-diaminocyclohexaneplatinum(II) (DDCP) and of sulfato-1,2-diaminocyclohexaneplatinum(II) (SHP) each induced lung adenomas in A/JAX mice, while cis-DDP also initiated skin papillomas in CD-1 mice. Cis-DCP and cis-dichlorobis(pyrrolidine)platinum(II) induced sarcomas at the injection site in rats. Each of the above complexes was mutagenic for Salmonella typhimurium TA100, and the mutagenicity of the SHP and DDCP complexes was highly dependent on the stereoconfiguration of the 1,2-diaminocyclohexane ligand. No quantitative correlation of mutagenicity or tumorigenicity with electrophilic reactivity (as determined by reaction with DNA) or reported antitumor activity was found for the DDP, DDCP, and SHP complexes. The mutagenic and carcinogenic properties of S-vinylhomocysteine (vinthionine) were examined in relation to those of S-ethylhomocysteine (ethionine) to test a hypothesis that vinthionine might be a proximate carcinogenic form of ethionine. (no Refs)

6. SPECIES DIFFERENCES IN MUTAGENICITY, COVALENT PROTEIN BINDING AND NEPHROTOXICITY OF THE FLAME RETARDANT TRIS(2,3-DIBROMOPROPYL) PHOSPHATE (MEETING ABSTRACT).

Soderlund E, Dybing E, Nelson SD
Department of Toxicology, National Institute of Public Health, Olso, Norway
Acta Pharmacol Toxicol; 49(Suppl1):48 1981

Tris(2,3-dibromopropyl)phosphate (Tris-BP), the major flame retardant formerly used in US sleepwear, is a potent mutagen, a nephrocarcinogen and an acute nephrotoxin. Hepatic microsomes from rats, mice, hamsters, and guinea pigs are all able to activate Tris-BP to mutagenic products in the Salmonella microsome quantitative reversion assay, mice microsomes being the most and guinea pig microsomes the least active. Phenobarbital (PB)-pretreatment increases the mutagenic activity with all microsomal preparations, whereas 3-methylcholanthrene (MC)-pretreatment decreases Tris-BP mutagenicity in rats and mice and gives a moderate increase in hamsters and guinea pigs. Hepatic microsomes from all species tested have approx similar basal capabilities in converting Tris-BP to covalently protein bound products in vitro; PB-pretreatment increases binding rates in all preparations, MC-pretreatment increases Tris-BP covalent binding with hamster and guinea pig microsomes but not with microsomes from rat or mouse liver. Tris-BP binds covalently to liver protein in vivo in all species and to kidney protein in hamster, guinea pig and mouse to the same degree. In rat kidneys, on the other hand, seven fold higher protein binding levels are found compared to liver, correlating with the finding that kidney is the target organ in this species. None of the other species showed any Tris-BP-induced kidney damage. (no Refs)

7. POTENCY OF AFLATOXIN B1 AND AFLATOXIN M1 IN CYTOTOXICITY AND DNA REPAIR ASSAYS (MEETING ABSTRACT).

Green CE, Rice DW, Hsieh DP, Byard JL
Department of Environmental Toxicology, University of California, Davis, CA, 95616
Toxicologist; 1(1):42 1981

Although the acute toxicity and carcinogenicity of aflatoxin B1 (AFB1) has been thoroughly documented, relatively little is known of the potency of aflatoxin M1 (AFM1), a hydroxylated metabolite of AFB1. Therefore, the cytotoxicity and genotoxicity of AFB1 and AFM1 were compared using in vitro system of primary cultures of rat hepatocytes. Hepatocytes were cultured for 20 hr (2.5 x 10(6) cells/dish) in hormone supplemented culture medium. The incubation was continued for an additional 24 hr with the test chemicals and 0.5 uCi/ml [3H] thymidine ([3H]TdR). Cytotoxicity was assessed by measuring lactate dehydrogenase released into the culture medium. Both AFB1 and AFM1 were potent cytotoxins. LDH levels were elevated significantly above controls for AFB1 at 0.1 ug/dish and for AFM1 at 0.6 ug/dish. However, LDH concentrations rose to the same max of approx 200% of controls for AFB1 and AFM1 at a dose of 1.2 ug/dish. Genotoxicity was assessed by measuring unscheduled DNA synthesis by two different methods, incorporation of [3H] TdR into trypsin-resistant acid-precipitable material and autoradiographic analysis. AFB1 and AFM1 were both positive and about equally potent in the DNA repair assay using either technique. In vivo experients indicate a higher level of DNA binding for AFb1 than AFM1. There are two plausible explanations for the DNA repair data; 1) AFB1 and AFM1 bind to DNA to approx the same extent in the hepatocyte culture system, 2) less AFM1 is covalently bound to DNA than AFB1 but AFM1 adducts are more efficiently repaired. (1 Ref)

8. MUTAGENICITY OF ALKYL GLYCIDYL ETHERS IN THREE SHORT-TERM ASSAYS.

Thompson ED, Coppinger WJ, Piper CE, McCarroll N, Oberly TJ, Robinson D
Miami Valley Lab., Procter and Gamble Co., P.O. Box 39175, Cincinnati, OH, 45247
Mutat Res; 90(3):213-231 1981

Effect of alkyl chain length on the mutagenic potential of glycidyl ethers was examined in three in vitro assays, the Salmonella/mammalian microsome assay, the L5178Y mouse lymphoma assay, and by unscheduled DNA synthesis induced in WI38 human diploid fibroblasts. Glycidol, ethyl glycidyl et her, butyl glycidyl ether, and hexyl glycidyl ether were positive in the Salmonella revertant assay with or without metabolic activation, although enhancement of the response was seen in the presence of S9. Octyl glycidyl ether, decyl glycidyl ether, and dodecyl glycidyl ether induced a weak mutagenic response only in the presence of S9. Tetradecyl glycidyl ether was negative in this assay. In the mouse lymphoma assay, glycidol and the ethyl, butyl, and hexyl glycidyl ethers gave positive responses with or without S9. Octyl, dodecyl, and tetradecyl glycidyl ethers were negative. In the unscheduled DNA synthesis assay, positive responses were obtained for glycidol and ethyl glycidyl ether in the presence of S9. Weak responses were obtained for glycidol and ethyl glycidyl ether in the presence of S9. Weak responses were obtained for butyl glycidyl ether with S9 and ethyl glycidyl without S9, but other compounds were negative in this assay. (18 Refs)

9. MUTAGENICITY OF A SERIES OF HEXACOORDINATE CHROMIUM(III) COMPOUNDS.

Warren G, Schultz P, Bencroft D, Bennett K, Abbott EH, Rogers S
Dept. Chemistry, Montana State Univ., Bozeman, MT, 59717
Mutat Res; 90(2):111-118 1981

A series of 17 substitutionally inert chromium(III) compounds were synthesized and their genetic toxicity investigated in a differential DNA repair assay (DR) or the Salmonella histidine reversion assay (Ames assay). Genetic toxicity in both systems was critically dependent upon the ligand composition of the chromium(III) complexes. Compounds tested showed a parallel between mutagenicity in the Ames test in Salmonella and differential inhibition in the DR test in Escherichia coli. The greater the differential inhibition in the repair test, the more likely it was that a compound would be mutagenic in the Salmonella system. Four of the 17 compounds tested were positive in both systems, while 4 compounds were less active in the repair assay and negative in the Ames test. The remaining nine were negative in both assays. Three of the four most active complexes had four stable aromatic amine ligands, a charge of plus one, and two more labile ligands in a cis-configuration. Chromium(III) in the proper ligand environment can have considerable genetic toxicity and could represent one of the several possible ultimate species in a mechanism for chromium mutagenesis and carcinogenesis. (36 Refs)

10. CHARACTERIZATION OF DNA REPAIR ELICITED BY CARCINOGENS AND DRUGS IN THE HEPATOCYTE PRIMARY CULTURE/DNA REPAIR TEST.

McQueen CA, Williams GM
(c/o Williams), American Health Foundation, 1 Dana Road, Valhalla, NY, 10595
J Toxicol Environ Health; 8(3):463-477 1981

Autoradiographic unscheduled DNA synthesis measured in the hepatocyte primary culture/DNA repair test after exposure to chemical carcinogens was characterized. Replicated and nonreplicated hepatocyte DNA was separated by CsCl gradient centrifugation. Uptake of 3H-thymidine into nonreplicated DNA was seen after exposure of hepatocytes to the activation-independent carcinogen methyl methanesulfonate or the activation-dependent carcinogen N-2-acetylaminofluorene, but not with fluorene, a noncarcinogen. N-4-acetylaminofluorene, a mutagen with uncertain carcinogenicity, also elicited DNA repair. Density gradient centrifugation allowed the detection of DNA repair in hepatocytes following exposure to the antihistamines pyrilamine maleate and tripelennamine HCl. Methapyrilene did not elicit repair. (44 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN VERTEBRATES

11. APHIDICOLIN DOES NOT INHIBIT DNA REPAIR SYNTHESIS IN ULTRAVIOLET-IRRADIATED HELA CELLS: A RADIOAUTOGRAPHIC STUDY.

Hardt N, Pedrali-Noy G, Focher F, Spadari S
Departement de Biologie Moleculaire, Universite Libre de Bruxelles, Brussels, Belgium
Biochem J; 199(2):453-455 1981

A radioautographic examination of nuclear DNA synthesis in unirradiated and UV-irradiated HeLa cells, in the presence and in the absence of aphidicolin showed that aphidicolin inhibits nuclear DNA replication and has no detectable effect on DNA repair synthesis. Although the results establish that in uv-irradiated HeLa cells most of the DNA repair synthesis is not due to DNA polymerase alpha, they do not preclude a significant role for this enzyme in DNA repair processes. (Author abstract) (31 Refs)

12. ABNORMAL RECOVERY OF DNA REPLICATION IN ULTRAVIOLET-IRRADIATED CELL CULTURES OF DROSOPHILA MELANOGASTER WHICH ARE DEFECTIVE IN DNA REPAIR.

Brown TC, Boyd JB
(c/o Boyd) Dept. Genetics, Univ. California, Davis, CA, 95616
MGG; 183(2):363-368 1981

Cell cultures prepared from embryos of a control stock of Drosophila melanogaster respond to UV light with a decline and subsequent recovery both of thymidine incorporation and in the ability to synthesize nascent DNA in long segments. Recovery of one or both capacities is absent or diminished in irradiated cells from 10 nonallelic mutants that are defective in DNA repair and from four of five nonallelic mutagen-sensitive mutants that exhibit normal repair capabilities. Recovery of thymidine incorporation is not observed in 9 of 10 DNA repair-defective mutants. On the other hand, partial or complete recovery of incorporation is observed in all but one repair-proficient mutagen-sensitive mutant. Irradiated cells from two mutants that display no excision capacity exhibit a gradual arrest of thymidine incorporation within 20 hr after the initial decline. this arrest of incorporation is not observed in mutants exhibiting only partial defects in excision repair. Recovery of the ability to synthesize nascent DNA in long segments is normal in cells from the two mutants that display no excision capacity, indicating that recovery does not depend upon the excision of pyrimidine dimers from cellular DNA. Recovery of that ability is not observed, however, in cells from one partially excision-defective mutant, two of three postreplication repair-defective mutants, two of four mutants defective in both excision and postreplication repair, and one of five repair-proficient mutagen-sensitive mutants. These results indicate that recovery of normal DNA replication in irradiated Drosophila cells depends upon the activity of several functions. (Author abstract) (17 Refs)

13. DNA LESIONS AND CHROMOSOMAL ALTERATIONS (MEETING ABSTRACT).

Natarajan AT, Van Zeeland AA
Laboratory of Radiation Genetics and Chemical Mutagenesis, University of Leiden, Leiden, The Netherlands
Int J Radiat Biol; 40(2):205 1981

Physical and chemical mutagens induce primary lesions in DNA which are subjected to cellular repair. Unrepaired or mis-repaired lesions give rise to chromosomal alterations. The types and frequencies of DNA lesions induced by diverse mutagens are various and it is not clear to which types of lesions lead to chromosomal aberrations. We have examined this question, with regard to the chromosomal aberrations, induced by ionizing radiations and short wave UV, in great detail, by quantifying primary lesions and genetic effects. These studies indicate that the DNA double-strand break is the major lesion responsible for chromosomal aberration induced by ionizing radiations. Pyrimidine dimers seem to be lesions responsible for induction of sister chromatid exchanges, chromosomal aberrations, cell killing as well as point mutations, following short wave UV treatment. (4 Refs)

14. QUANTITATION OF THE REPAIR OF GAMMA-RADIATION-INDUCED DOUBLE-STRAND DNA BREAKS IN HUMAN FIBROBLASTS.

Woods WG
Dept. Pediatrics, Univ. Minnesota Hosp., Box 454 Mayo Memorial Building, Minneapolis, MN, 55455
Biochim Biophys Acta; 655(3):342-348 1981

The quantitation and repair of double-strand DNA breaks in human fibroblasts has been determined using a method involving the nondenaturing elution of DNA from a filter. DNA from cells from two human fibroblast lines exposed to gamma-radiation from 0 to 10,000 rad showed increasing retention on a filter with decreasing radiation dose, and the data suggest a linear relationship between double-strand breaks induced and radiation dose. The ability of normal human fibroblasts to repair double-strand breaks with various doses of radiation was demonstrated, with a t1/2 of 10 min for repair of 5,000 rad exposure and 39 min for repair of 10,000 rad damage. The kinetics of the DNA rejoining were not linear and suggest that, as in the repair of single-strand breaks, both an initial 'fast' and a later 'slow' mechanism may be involved. (Author abstract) (17 Refs)

15. CHARACTERIZATION OF THE HEPATIC DNA DAMAGE CAUSED BY 1,2-DIBROMOETHANE USING THE ALKALINE ELUTION TECHNIQUE.

White RD, Sipes IG, Gandolfi AJ, Bowden GT
(c/o Sipes) Dept. Anesthesiology, Arizona Health Sciences Center, Univ. Arizona, Tucson, AZ, 85724
Carcinogenesis; 2(9):839-844 1981

Hepatic lesions induced by 1,2-dibromoethane (EDB: 25-75 mg/kg, ip) in male Swiss Webster mice were assessed by a modified alkaline elution assay. The major changes were use of 47-mm diameter filters and a microfluorometric technique to quantify the DNA. EDB administration caused a dose-dependent increase in DNA strand breaks. Allowing the DNA sample to remain on the filter in the presence of pH 12.3 buffer facilitated the conversion of alkali-labile sites to strand breaks detectable by the alkaline elution technique. To determine the presence of DNA cross-linking after EBD exposure, one-half of the hepatic nuclei were x-irradiated (200 rads) at 0 C. No EBD-induced DNA-DNA or DNA-protein cross-links were detected. This method may be useful for studying the nature of DNA damage induced by in vivo carcinogens. (22 Refs)

16. THE INFLUENCE OF BIOLOGICAL AND CHEMICAL FACTORS ON THE INDUCTION OF DNA DOUBLE-STRAND BREAKS BY RADIATION (MEETING ABSTRACT).

Chadwick KH, Leenhouts HP
Association Euraton-ITAL, Postbus 48, Wageningen, The Netherlands
Int J Radiat Biol; 40(2):260 1981

One of the problems connected with the association of the DNA double-strand break to the biological effect of radiation and the linear-quadratic dose relationship to the production of DNA double-strand breaks has been the probability that two independently induced single-strand breaks will combine to form a double-strand break. Evidence will be presented which indicates that different chemical species are involved in the induction of the linear and quadratic components of dose-effect relationships. Recent evidence will be presented showing that the immediate linear dose-effect relationships. Recent evidence will be presented showing that the immediate linear dose-response curve for double-strand break induction is converted within 3 hr to a linear-quadratic dose-response curve. The combination of this information indicates that both chemical and repair factors are involved in 'lining-up' two independently induced single-strand breaks to produce a double-strand break. (no Refs)

17. 3-AMINOBENZAMIDE STIMULATES UNSCHEDULED DNA SYNTHESIS AND REJOINING OF STRAND BREAKS IN HUMAN LYMPHOCYTES.

Bohr V, Klenow H
Biochemical Inst. B, Panum Inst., Univ. Copenhagen, Copenhagen, Denmark
Biochem Biophys Res Commun; 102(4):1254-1261 1981

The effects of 3-aminobenzamide (3AB) on DNA repair in human lymphocytes, L1210 cells, and sarcoma 180 ascites cells were examined by measuring both unscheduled DNA synthesis and the rejoining of strand breaks. 3AB (3 milliM) stimulated unscheduled DNA synthesis, as measured by 3H-thymidine incorporation, in UV-irradiated and dimethylsulfate (DMS)-treated human lymphocytes. At a similar concentration (2.5 milliM), this compound also stimulated the rejoining of DMS-induced strand breaks, as measured by alkaline elution procedures. In contrast, 3AB inhibited DNA repair in similarly treated L1210 and sarcoma 180 ascites cells. The effects of another inhibitor of poly(ADP-ribose) synthesis, nicotinamide, were similar to those of 3AB, indicating that there is a relationship between DNA repair and poly(ADP)ribose synthesis in these cell types. (12 Refs)

18. EFFECTS OF INHIBITORS OF DNA STRAND BREAK REPAIR ON HELA CELL RADIOSENSITIVITY (MEETING ABSTRACT).

Ward JF, Blakely WF, Joner EI
Division of Radiation Biology, School of Medicine, University of California, San Diego, La Jolla, CA, 92093
Conference on Chemical Modification: Radiation and Cytotoxic Drugs, September 17-20, 1981, Key Biscayne, Florida. Committee for Radiation Oncology Studies 139 pp., 1981.

In order to assess the relationship between radiation induced cell killing and DNA single strand break repair capability, we have examined the effects of drugs shown to inhibit the latter process on cell radiosensitivity. For determination of DNA strand break repair rates we have developed the Kohn alkaline elution assay so that we can measure repair after low radiation doses (1 Gray, Gy) reproducibly and accurately. Using this assay we have shown that there are at least two components of strand break repair in V79 cells. The fast component after 1.5 Gy has a half time of approx 3.2 min and the slow of approx 50 at 24C. The fast component repair process is slowed at higher doses of radiation. The protocol developed for drug exposure was designed to inhibit DNA repair for the first hr following radiation: Aliquots of log phase HeLa cells were cooled to 24C 1 hr prior to irradiation at which time the drug (Cytosine arabinoside, N-ethylmaleimide, dinitrophenol, or diamide) was added. Cells were irradiated at OC and then incubated at 24C for 1 hr post irradiation with drug. The drug was then removed and cells plated out at 37C for assay of survival in the normal way. DNA strand break repair was measured as a function of post irradiation time at 24C. We observed that all four drugs can inhibit the fast strand break repair process at concentrations which are not cytotoxic. For instance cytosine arabinoside slowed the rate of fast strand break repair by a factor of 3. Under drug conditions in which fast strand break repair is inhibited, cells are radiosensitized: 10(-4) M cytosine arabinoside reduces DO from 1.3 Gy to 0.75 Gy and Dq from

1.8 Gy to 1.3 Gy. Thus while the proposed molecular mechanisms of drug action (in causing inhibition of DNA synthesis) are different, their common effect in causing inhibition of DNA strand repair correlates to their abi lity to increase cell radiosensitivity. (2 Refs)

19. PROSTAGLANDIN SYNTHETASE CATALYZED DNA STRAND BREAKS BY AROMATIC AMINES (MEETING ABSTRACT).

Rahimtula A, Moldeus P, Nordenskjoeld M, Andersson B
Memorial University of Newfoundland, Newfoundland, Canada
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Several aromatic amines are renal medullary toxins and bladder carcinogens. We have found that the aromatic amines 2-naphthylamine, 2-4-diaminotoluene, p-aminophenol and p-phenetidine at a concentration of 50uM cause a 2-3 fold increase in DNA strand breaks in cultured human fibroblasts in the presence of sheep vesicular gland microsomes and arachidonic acid. Indomethacin and butylated hydroxyanisole inhibited this reaction. Curiously, benzidine did not give rise to a significant increase in DNA strand breaks. Metabolism of these amines by prostaglandin synthetase was judged by their ability to complete with and inhibit another prostaglandin synthetase dependent reaction - the activation of paracetamol. An 0.1 mM concentration of these amines inhibited the glutathione conjugate formation of paracetamol by 60-90%. Covalent protein binding of [3H]paracetamol was similarly inhibited. At the concentration used, these amines did not significantly affect the cyclooxygenase activity as judged by prostaglandin E2 and prostaglandin F2alpha formation. (2 Refs)

20. DNA STRAND BREAK DAMAGE (DSBD) IN HUMAN LEUKOCYTES EXPOSED TO A TUMOR PROMOTER: EFFECT OF ARACHIDONIC ACID AND OTHER AGENTS (MEETING ABSTRACT).

Birnboim HC
Atomic Engery of Canada Limited, Chalk River, Ontario, Canada
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

The tumor promoter, phorbol myristate acetate (PMA), is a powerful stimulator of the respiratory burst in phagocytic cells. We are postulating that products of the burst are intimately involved in skin tumor promotion. This hypothesis was proposed after we observed that PMA stimulation of human WBC rapidly leads to extensive DSBD, equivalent to 4-8 Gray (Gy) of gamma-irradiation. DSBD was monitored by a fluorometric method. DSBD is maximal after 40-45 min exposure to PMA at 37C. PMA-induced DSBD (PI-DSBD) is completely inhibited at 0C or by the addition of 2-deoxyglucose and partially inhibited by catalase or superoxide dismutase at 200 ug/mL. Arachidonic acid alone causes low levels of DSBD, but significantly reduces the level of PI-DSBD. Vitamin E also partially inhibits PI-DSBD but singlet oxygen scavengers do not. OH radical scavengers afford no protection at 50-100 mM, but at 0.5M dimethylsulfoxide and glycerol strongly protect. This is likely not due to OH scavenging activity since DMSO inhibits the respira tory burst at this concentration. Azide or cyanide cause a marked increase in PI-DSBD. PMA-stimulated human WBC can cause DSBD in mouse thymocytes when mixed in a 1:4 ratio if the latter inhibitors are present. Thus the evidence suggests that DNA in WBC can be damaged by a mechanism requiring both superoxide anion and H2O2, but probably not acting via OH radical. We suggest that phagocytic cells play a role in skin tumor promotion by virtue of their ability to prodice superoxide anion radical in response to PMA, and that superoxide anion radical in turn causes DNA damage in 'initiated' skin cells. (no Refs)

21. DIFFERENTIATED CELLS FROM BALB/C MICE DIFFER IN THEIR RADIOSENSITIVITY.

Rahmsdorf HJ, Ponta H, Bachle M, Mallick U, Weibezahn KF, Herrlich P
Kernforschungszentrum Karlsruhe, Institut fur Genetik und fur Toxikologie von Spaltstoffen, D-7500 Karlsruhe 1, W. Germany
Exp Cell Res; 136(1):111-117 1981

Various isolated cells of an inbred mouse strain (BALB/c) differed widely in their sensitivity to gamma irradiation: fibroblasts are 5 x more resistant than peripheral lymphocytes. Among lymphocytes, T cells are more resistant than B cells. Cell lines derived from the primary cells conserved their radiosensitivity. Cytofluorometric measurements show that the differential reaction of a cell to gamma irradiation can be detected already 2-3 hr after the irradiation event. Radiation-sensitive cells are delayed for a longer time in S phase and G2 phase of the cell cycle than radiation-resistant cells. No difference in the capacity of the cells to perform single-strand break repair, double-strand break repair or unscheduled DNA synthesis could yet be detected. (Author abstract) (24 Refs)

22. DNA-DAMAGE IN HUMAN CELLS TREATED WITH THE CLOSELY RELATED ALKYLATING AGENTS PEPTICHEMIO, M-L-SARCOLYSIN AND MELPHALAN.

Ringborg U, Lambert B, Lewensohn R, Turesson I
Radiumhemmet, Karolinska Hosp., S-104 01 Stockholm, Sweden
Eur J Cancer Clin Oncol; 17(9):991-996 1981

In vitro experiments were performed on human peripheral WBC to compare DNA repair synthesis induced by peptichemio (a multipeptide complex containing m-L-sarcolysin), m-L-sarcolysin and melphalan. The peptide bound m-L-sarcolysin gave rise to max DNA repair synthesis at a concentration interval between 1 x 10(-5) and 3 x 10(-5) M as opposed to a concentration interval of 3 x 10(-4) to 1 x 10(-3) M for melphalan. The peptide bound m-L-sarcolysin induced DNA repair synthesis at similar molar concentrations to m-L-sarcolysin alone. The difference between melphalan on one hand, and m-L-sarcolysin and peptichemio on the other hand, may reflect a more rapid uptake of the latter substances. Inhibition of 3H-uridine incorporation in human peripheral lymphocytes supports this hypothesis. The frequency of sister chromat id exchanges in human fibroblasts was significantly higher after treatment with m-L-sarcolysin compared to melphalan, a finding which also indicates that these chemically closely related substances modify the cellular DNA differently. When DNA repair synthesis was induced by UV light and methyl-methane-sulfonate (a monofunctional alkylating agent), no additional DNA repair synthesis was induced, if peptichemio, m-L-sarcolysin or melphalan was added. These results indicate that the repair of lesions induced by melphalan peptichemio, UV-light and methyl-methane-sulfonate is mediated by at least one common controlling enzyme. (Author abstract) (17 Refs)

23. PHOTOREPAIR OF PYRIMIDINE DIMERS IN HUMAN SKIN IN VIVO.

D'Ambrosio SM, Whetstone JW, Slazinski L, Lowney E
Dept. Pharmacology, Coll. Medicine, Ohio State Univ., Columbus, OH, 43210
Photochem Photobiol; 34(4):461-464 1981

The exposure of human skin in vivo to UV radiation emitted from a sunlamp induces the formation of pyrimidine dimers. The number of dimers, as detected by UV-endonuclease, decreases following exposure of the UV-irradiated skin to visible wavelengths of light. These results suggest that humans possess a mechanism by which pyrimidine dimers are photorepaired upon illumination of human skin in vivo with visible light. (Author abstract) (33 Refs)

24. POSTRADIATION DNA REPAIR IN PERIPHERAL BLOOD LEUKOCYTES OF RATS SUBJECTED TO WHOLE-BODY GAMMA IRRADIATION.

Grishchenko IuD, Remizova IV, Komar VE
Central Res. Roentgenoradiological Inst., Leningrad, USSR
Radiobiologiia; 21(4):503-507 1981

Analysis of the level of single-stranded DNA breaks in DNA from lymphocytes of male albino rats subjected to a single whole-body gamma-irradiation with 300, 600, or 1,200 rads showed DNA repair during the first 1 hr after irradiation. The second wave of DNA breaks was recorded 24 hr after irradiation. (11 Refs) (In RUS)

25. DISTRIBUTION OF DNA-BOUND CARCINOGEN 4-NITROQUINOLINE 1-OXIDE AND OF REPAIR-SYNTHESIZED DNA IN CHROMATIN OF WI-38 CELLS.

Nose K
Dept. Biochemistry, Toyama Medical and Pharmaceutical Univ. Sch. Medicine, Sugitani, Toyama 930-01, Japan
Cancer Lett; 14(2):205-215 1981

Distribution within chromatin of the binding sites of 4-nitroquinoline-1-oxide (NQ) was investigated. Binding of NQ to nucleic acids of cells treated in vitro (WI-38 human diploid fibroblasts) reached a plateau by 90 min at a concentration of 1 x 10(-5) M. The specific activity of (3H)NQ bound to DNA did not change significantly during digestion with DNAase I, whereas it decreased with increasing degradation of DNA by micrococcal nuclease. These results suggest that NQ preferentially binds to nucleosomal linker DNA; no correlation is apparent between transcriptional activity of chromatin and bindin g of NQ to DNA. When the distribution of repair-synthesized DNA in chromatin damaged by NQ was studied, (3H)thymidine incorporated into repaired DNA was found to be more sensitive to nucleases but distributed approx equally among chromatin subfractions of differing transcriptional activity. (35 Refs)

26. A STUDY OF THE EFFECTS OF 1-METHYL-1-NITROSOUREA (MNU) ON THE PHYSICAL PROPERTIES OF CHROMATIN IN THE GUINEA PIG PANCREAS (MEETING ABSTRACT).

Yang P, Woolley PV
Division of Medical Oncology, Georgetown University Medical Center, Washington, DC, 20007
Newsletter Natl Pancreas Cancer Project; VI(2):67 1981

The literature indicates that carcinogens can alter the physical state of chromatin in target tissues. As a part of the study of carcinogen effects upon the pancreas and other organs, we have examined the effect of MNU administration on the thermal melting and circular dichroism spectra of pancreas and liver chromatin. Oligomeric chromatin (av DNA size 2000 base pairs) was isolated from purified nuclei by a mild nuclease digestion, followed by a 5-20% linear sucrose gradient centrifugation, and was dialyzed into 1mM Tris, pH 8 for examination of thermal melting. The melting curves were broad and when expressed in derivative form showed several distinct melting regions, with Tm values of 56, 64 and 78 C. When animals were treated with 10 mg/kg MNU, there was no effect on either the thermal melting profile or the circular dichroism spectrum of pancreatic chromatin, but with 60 mg/kg three x in eight days, there were definite shifts of melting towards lower temperatures. The effect was more pronounced in the pancreas than in the liver. There were small concurrent changes in the circular dichroism spectra. The data indicate that MNU can produce alterations in the physical state of pancreatic chromatin and that the pancreas may be more easily damaged than the liver. (no Refs)

27. CHEMICAL CARCINOGENESIS IN THE RAT: COMMON MODE OF ACTION OF CARCINOGENS AT THE CHROMOSOME LEVEL.

Sugiyama T, Ueda N, Maeda S, Shiraishi N, Goto-Mimura K, Murao S, Chattopadhyay SC
Dept. Pathology, Kobe Univ. Sch. Medicine, Chuo-ku, Kobe, Japan 650
JNCI; 67(4):831-839 1981

The chromosomal distribution of chromosome aberrations (CA) and sister chromatid exchanges (SCE) induced by various chemical carcinogens such as 7,12-dimethylbenz[a]anthracene, 7,8,12-trimethylbenz[a]anthracene, 1-butyl-1-nitrosourea, urethan, 4-nitroquinoline 1-oxide, 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide, and the antineoplastic compound mitomycin C was studied with the use of noninbred Long-Evans male rat bone marrow cells in vivo and in vitro. The CA and SCE induced by these structurally different chemicals were distributed in similar pattern among and along chromosomes when the chemicals were given a short time (6 hr) before the metaphase cells were harvested. The specific distribution pattern of chemically induced CA and SCE along chromosomes was attributed to the late DNA replication of the vulnerable chromosome regions. Conversely, x-ray-induced CA were distributed more randomly. Thus the different chemical carcinogens were shown to exert a similar genetic effect at the chromosome level. (Author abstract) (38 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN BACTERIA

28. GENOME MULTIPLICITY AND RADIATION RESISTANCE IN MICROCOCCUS RADIODURANS.

Harsojo, Kitayama S, Matsuyama A
Centre for Application of Isotopes and Radiation, Kebayoran Lama, Jakarta Selatan, Indonesia
J Biochem (Tokyo); 90(3):877-880 1981

The number of genome equivalents of DNA per cell of M radiodurans changed from approx 5 to 10 depending on the media used. The sensitivity to UV light or gamma-rays was not different between the cells with different genome multiplicity. This suggests that the efficient repair process for DNA damage

expressed in M radiodurans is not influenced by the multiplicity of genomes in a cell. (Author abstract) (24 Refs)

29. MUCH OF SPONTANEOUS MUTAGENESIS IN ESCHERICHIA COLI IS DUE TO ERROR-PRONE DNA REPAIR: IMPLICATIONS FOR SPONTANEOUS CARCINOGENESIS.

Sargentini NJ
Dept. Radiology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
Carcinogenesis; 2(9):863-872 1981

The roles of DNA excision repair and genetic recombination in spontaneous mutagenesis were examined in Escherichia coli DNA repair mutants. Spontaneous mutation rates per bacterium per cell were determined for the reversion of ochre nonsense (UAA: his-4 and trpE65), amber nonsense (UAG: lacZ3), and frameshift (trpE9777) mutations and for forward mutations to valine resistance. Depending on the assay system, uvrA and uvrB mutations enhanced mutagenesis 1.9-to 6.2-fold in minimal growth medium. Complex growth medium enhanced mutagenesis in uvr+ but not uvrB strains. Mutations that inhibit error-prone DNA repair, ie, lexA, recA, umuC, or recB and uvrD in combination, reduced spontaneous mutagenesis levels in the uvrA and uvrB strains. The lexA and recA mutations also reduced spontaneous mutagenesis in uvr+ strains. Effects of the DNA repair genes on UV radiation mutagenesis were qualitatively similar to their effects on spontaneous mutagenesis. These results suggested that significant levels of mutagenic damage (and carcinogenic damage) may be produced by normal metabolic processes in cells. (63 Refs)

MACROMOLECULAR BINDING OF CARCINOGENS

30. IMMUNOCYTOLOGICAL DETECTION OF AAF-DNA ADDUCTS IN HELA CELL NUCLEI.

Sage E, Gabelman N, Mendez F, Bases R
(c/o Bases) Dept. Radiology, Albert Einstein Coll. Medicine, Bronx, NY, 10461
Cancer Lett; 14(2):193-204 1981

Rabbit antibodies for acetylaminofluorene (AAF)-guanosine and for DNA modified b y the presence of AAF adducts were utilized. HeLa cells growing in suspension at 2.5 x 10(5)/ml were exposed to increasing concentrations of N-acetoxy-AAF in dimethylsulfoxide at less than 0.5% final concentration. Dose-dependent increase in the proportion of immunoreactive cells in cultures exposed to carcinogen for 15 min at 37 C was observed. When the time course of disappearance of nuclear immunoreactivity toward anti-AAF-DNA was compared with the loss of radiolabel in cells exposed to 5 ug/ml of labeled N-acetoxy-AAF, nuclear immunoreactivity was induced but then declined rapidly for 5 hr. The total radiolabel in purified nuclear DNA declined much more slowly. In the first 3 hr after removal of carcinogen, the induced immunoreactivity was rapidly lost with no significant reduction in labeled DNA or in the dominant adduct fraction, N-(deoxyguanosin-8-yl)-2-aminofluorene (dG-C8-AAF). In the next 3 hr loss of immunoreactivity was insignificant but the drop in acetylated C-8 adducts was dramatic. Radiolabel experiments indicated that most adducts were still within the nucleus but did not react with antibody. It is suggested that DNA-AAF adducts become inaccessible to antibody due to the mechanics of the repair process. (33 Refs)

31. METABOLISM AND MACROMOLECULAR BINDING OF THE CARCINOGEN MICHLER'S KETONE IN RATS.

Struck RF, Shih TW, Johnston TP, Kirk MC, Hill DL
Kettering-Meyer Lab., Southern Res. Inst., Birmingham, AL, 35255
Xenobiotica; 11(8):569-577 1981

Studies on the metabolism of 14C-Michler's ketone (4,4'-bis-(dimethylamino)[carbonyl-14C]benzophenone) in rats have revealed that this carcinogen is subject to demethylation, ring-hydroxylation and N-acetylation after adjacent methyl groups have been removed. As identified by mass spectral analysis, microsomal metabolites are the mono-, di-, tri- and tetra-demethylated derivatives. The major metabolites appearing in the bile are the di- and tri-demethylated derivatives and the N-acetylated tetra-demethylated compound; minor metabolites, tentatively identified, are the ring-hydroxylated derivatives of di- and tri-demethylated Michler's ketone and of N-acetylated tri- and tetra-demethylated Michler's ketone. The major urinary metabolite is tentatively identified as a ring-hydroxylated derivative of N-acetylated, di-demethylated Michler's ketone; a minor urinary metabolite lacks the hydroxyl group. Injection of 14C-Michler's ketone into rats resulted in the irreversible binding of radioactivity to liver proteins. When the rats were pretreated with phenobarbital, this binding was increased and extended to proteins of some other tissues and to DNA and RNA of liver and DNA of kidney. (Author abstract) (13 Refs)

32. IN VITRO AND IN VIVO COVALENT BINDING OF THE KIDNEY TOXICANT AND CARCINOGEN TRIS(2,3-DIBROMOPROPYL)-PHOSPHATE.

Soderlund EJ, Nelson SD, Dybing E
Dept. Toxicology, Natl. Inst. Public Health, Postuttak, Oslo 1, Norway
Toxicology; 21(4):291-304 1981

Incubation of 3H-tris(2,3-dibromopropyl)-phosphate (TRIS-BP) with rat liver microsomes led to its activation to products which bound covalently to microsomal protein. The reaction was NADPH-dependent, and boiled microsomes yielded no binding. The reaction could be inhibited by nitrogen; carbon monoxide, which inhibits cytochrome P-450-mediated reactions, also reduced binding rates significantly. SKF 525-A and metyrapone, a selective inhibitor of phenobarbital-inducible cytochrome P-450, inhibited TRIS-BP activation. Alpha-napthoflavone, a selective inhibitor of cytochrome P-448, had little effect. Addition of glutathione and N-acetylcysteine markedly inhibited binding, but ascorbic acid did not. Paraoxon, an esterase inhibitor, and 1,1,1-trichloropropene-2,3-epoxide and cyclohexene oxide also were without effect. Rat kidney microsomes were capable of activating TRIS-BP to 8% of the level achieved by rat liver microsomes. Administration of TRIS-BP to rats resulted in considerable binding to kidney proteins, with lesser amounts detected in liver and very little in muscle proteins. Liver microsomes activated TRIS-BP to bind to DNA in vitro, but kidney microsomes did not. (31 Refs)

33. THE BINDING OF 7,12-DIMETHYLBENZ[A]ANTHRACENE TO MAMMARY GLAND MACROMOLECULES IN THE HAMSTER: EFFECTS OF ENOVID FEEDING OR TRANSPLACENTAL EXPOSURE TO DIETHYLSTILBOESTROL.

Hertzog PJ, Lawson TA, Gingell R

Cancer Res. Unit, Univ. York, Heslington, York YO1 5DD, England

Chem Biol Interact; 37(1):199-205 1981

The covalent binding of 7,12-[3H]dimethylbenz[a]anthracene ([3H]DMBA) to mammary gland macromolecules was studied in hamsters fed a contraceptive mixture, Enovid, those exposed transplacentally to diethylstilbestrol (DES), and controls. Compared with rats, hamsters are relatively resistant to DMBA mammary carcinogenesis, but susceptibility is increased by either of the above treatments with Enovid or DES. The amount of DMBA bound to DNA and protein was 4-5x greater than to RNA, but only DNA binding was persistent. Fifty-three percent of the DNA-bound DMBA was still present after 8 days. The amount of DMBA bound to hamster mammary DNA and its persistence was similar to that found in rats. Neither Enovid nor DES treatment altered the levels of binding to mammary macromolecules, nor their persistence. These results indicate that the species differences in the susceptibility to DMBA-induced mammary carcinogenesis in hamsters and rats, and modification of the former by hormones, is not due to differences in the activation of carcinogens. The role of hormones such as prolactin in the promotion phase of mammary gland carcinogenesis may explain these differences. (Author abstract) (18 Refs)

34. THE INVOLVEMENT OF PROSTAGLANDIN INTERMEDIATES IN COVALENT BINDING TO NUCLEIC ACIDS AND IN AGEING PIGMENT FORMATION (MEETING ABSTRACT).

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Department of Biochemistry, Memorial University of Newfoundland, Newfoundland, Canada

International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Eling et al 1979 have shown that incubation of 1-C14 arachidonic acid with the microsomes of platelets, guinea pig lung, rabbit kidney and rat stomach fundus results in substantial binding to the protein. We also find that prostaglandin synthetase catalyzes the binding of arachidonate to exogenous DNA and RNA to form a fluorescent product. Prostaglandin could therefore play some role in carcinogenesis. The binding of prostaglandin intermediates to microsomal protein resulted in extensive crosslinking and polymerization of some proteins. This was prevented by glutathione or antioxidants and suggests that free radicals were involved. The formation of fluorescent products in the microsomes was attributed to conjugated schiff base product formation from the reaction between phospholipid amines and aldehyde. The spectra was similar to lipofuscin. In vivo lipofuscin pigment formation has been associated with aging, vitamin E deficiency, polyunsaturated fatty acid feeding and the ingestion of various environmental xenobiotics. The various tissues involved were lung, liver, heart, spleen, brain, kidney and testis. Incubation of the microsomes from these tissues with arachidonate resulted in protein polymerization and fluorescence formation. (no Refs)

35. 32P-LABELING TEST FOR DNA DAMAGE.

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Proc Natl Acad Sci USA; 78(10):6126-6129 1981

Covalent adducts formed by the reaction of DNA with chemical carcinogens and mutagens may be detected by a 32P-labeling test. DNA preparations exposed to chemicals known to bind covalently to DNA [N-methyl-N-nitrosourea, dimethyl sulfate, formaldehyde, beta-propiolactone, propylene oxide, streptozotocin, nitrogen mustard, and 1,3-bis(2-chloroethyl)-1-nitrosourea] were digested to a mixture of deoxynucleoside 3'-monophosphates by incubation with micrococcal endonuclease (EC 3.1.31.1) and spleen exonuclease (EC 3.1.16.1). The digests were treated with [gamma-32P]ATP and T4 polynucleotide kinase (ATP:5'-dephosphopolynucleotide 5'-phosphotransferase, EC 2.7.1.78) to convert the monophosphates to 5'-32P-labeled deoxynucleoside 3',5'-bis-phosphates. These compounds were then separated on polyethyleneimine-cellulose thin layers in ammonium formate and ammonium sulfate soln. Autoradiograms of the chromatograms obtained by this high-resolution procedure showed the presence of nucleotides derived from chemically altered, as well as normal, DNA constituents. Maps from DNA exposed to any of the chemicals used exhibited a spot pattern typical for the particular chemical. This method detected a single adduct in 10(5) DNA nucleotides without requiring that the compound under investigation be radioactive and thus provides a useful test to screen chemicals for their capacity to damage DNA by covalent binding. (Author abstract) (41 Refs)

36. INTERACTION OF REDUCED MISONIDAZOLE WITH GUANOSINE AND DNA (MEETING ABSTRACT).

Varghese AJ, Whitmore GF

Ontario Cancer Institute, Toronto, Ontario, M4X 1K9, Canada

Conference on Chemical Modification: Radiation and Cytotoxic Drugs, September 17-20, 1981, Key Biscayne, Florida. Committee for Radiation Oncology Studies 139 pp., 1981.

One possible mechanism for the toxicity of misonidazole to mammalian cells under hypoxic conditions is the modifications of cellular macromolecules such as DNA, RNA and protein by reactive reduction metabolites of the drug. This is supported by the detection of radioactivity in the DNA, RNA and protein fractions of Chinese hamster ovary cells incubated with [14C] misonidazole under hypoxic conditions. UV absorption studies have confirmed that the misonidazole residue in these macromolecular fractions has undergone reduction of the nitro group. In order to further elucidate the nature of the interaction, we have prepared two of the primary reduction products of misonidazole, the hydroxylamine and the amine and their properties have been studied. While biological toxicity if any, of these products has yet to be demonstrated, the hydroxylamine was found to react with bovine albumin and DNA. This reaction was further investigated using guanosine, which reacted readily, as a model compound. The optimum pH for the reaction was pH 6.8. High-pressure liquid chromatographic separation of the reaction mixture indicated the presence of two major guanosine products. When [2-14C] misonidazole was used for these studies the major guanosine products were found to be non-radioactive indicating that the modification of guanosine does not involve simple addition of the two molecules. (no Refs)

37. STRUCTURAL IDENTIFICATION OF THE PROTEIN COVALENT ADDUCT FORMED IN VIVO IN RAT LIVER AFTER THIOACETAMIDE TREATMENT (MEETING ABSTRACT).

Dyroff MC, Neal RA
Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, TN. 37232
Toxicologist; 1(1):1 1981

Thioacetamide is a much studied hepatocarcinogen which previously has been reported to bind covalently to cellular macromolecules in vivo and after metabolism in vitro. This investigation addressed the problem of structural identification of the protein adduct which is formed in vivo in rat liver after thioacetamide administration. The subcellular distribution of radiolabeled thioacetamide indic ated that the microsomal fraction had significantly higher levels of covalently bound material than did the nuclear, mitochondrial, or cytosolic fractions which had nearly identical levels when expressed on a per mg protein basis. Pretreatment of the rats with either 3MC or PB did not significantly alter the amount or th subcellular distribution of covalently bound radioactivity from control values. The covalent adducts to amino acids were isolated from cytosolic protein by enzymatic digestion followed by ion exchange chromatography. Seventy percent of the covalently bound material eluted as a single peak between proline and glycine on an amino acid analyzer. Acid hydrolysis of the purified adduct released lysine and radiolabeled acetate quantitatively. The purified adduct and a standard of N-6-acetyl-lysine co-chromatographed on an amino acid analyzer and on gas chromatography. The isolated adduct and the standard had identical mass spectra. Thus the major protein adduct formed by thioacetamide in vivo is N-6-acetyl-lysine. (no Refs)

38. IN VITRO METABOLISM OF ACRYLONITRILE TO 2-CYANOETHYLENE OXIDE, REACTION WITH GLUTATHIONE, AND IRREVERSIBLE BINDING TO PROTEINS AND NUCLEIC ACIDS.

Guengerich FP, Geiger LE, Hogy LL, Wright PL
Dept. Biochemistry and Center in Environmental Toxicology, Vanderbilt Univ. Sch. Medicine, Nashville, TN, 37232
Cancer Res; 41(12):4925-4933 1981

The metabolism of the suspected carcinogen acrylonitrile was studied using subcellular fractions isolated from rats and humans. Irreversible binding of radioactive label from [1-14C]- or [2,3-14C]acrylonitrile to protein and DNA was enhanced by reduced nicotinamide adenine dinucleotide phosphate in the presence of rat liver microsomes or a reconstituted cytochrome P-450 system. During the reduced nicotinamide adenine dinucleotide phosphate-dependent reaction, HCN was produced, and the heme of cytochrome P-450 was destroyed. Rat brain microsomes did not produce detectable levels of metabolites. Conclusive evidence of metabolically mediated binding of acrylonitrile to protein and DNA in human systems was not found. With rats, metabolism was induced by pretreatment of animals with either phenobarbital or 5,6-benzoflavone. Labeled 2-cyanoethylene oxide was found to bind irreversibly to calf thymus DNA and microsomal protein. The extent of binding was greater in the case of 2,3-14C-labeled than 1-14C-labeled material. The relative first-order rate of acrylonitrile binding to calf thymus DNA in rat liver microsomal systems was one to two orders of magnitude less than that for 1,1,2-trichloroethylene and three orders of magnitude less than that for vinyl chloride or vinyl bromide. Rat liver microsomes or a reconstituted cytochrome P-450 system catalyzed the mixed-function oxidation of acrylonitrile to 2-cyanoethylene oxide. 2-Cyanoethylene oxide has a half-life of about 2 hr in neutral buffer at 37 C. This epoxide was found to serve as a substrate for microsomal epoxide hydrolase. HCN was released during hydrolysis of 2-cyanoethylene oxide or reaction of the epoxide with reduced glutathione; however, HCN release in either case was not stoichiometric with epoxide disappearance. 2-Cyanoethylene oxide reacted less rapidly with reduced glutathione than did acrylonitrile. Rat liver cytosol preparations contained glutathione S-transferase activity towards acrylonitrile and greater activity with 2-cyanoethylene oxide as a substrate. Cytosol preparations from rat brain and human liver had no detectable glutathione S-transferase activity towards acrylonitrile but did exhibit some activity towards 2-cyanoethylene oxide. These studies establish the basic pathways involved in the metabolism of acrylonitrile and should provide a basis for examination of the relevance of these individual steps and their roles in bioactivation and detoxication under more physiological situations. (Author abstract) (40 Refs)

39. THE EFFECT OF RADIOSENSITIZERS AND OXYGEN ON IRRADIATION OF BIOLOGICALLY ACTIVE DNA (MEETING ABSTRACT).

Lafleur MV, Pluijmackers EJ, Loman H
Department of Biophysics, Physics Laboratory of the Vrije Universiteit, Amsterdam, The Netherlands
Int J Radiat Biol; 40(2):208 1981

Aqueous soln of biologically-active single-stranded phi X174 DNA were irradiated with gamma rays in the presence of electron-affinic sensitizers. With misonidazole, nifuroxime and paranitroacetophenone no sensitization of the radiation-induced inactivation of the DNA could be detected. Quantitatively, these compounds act like ordinary scavengers. Metronidazole even protects the DNA much more than could be inferred from its reactivity with water radicals. Also the effect of radiation on DNA, dissolved in a low mol wt bacterial extract, was studied. The results show that oxygen induces sensitization of DNA inactivation for both double-stranded (RF) and single-stranded phi X174 DNA. Misonidazole also induces sensitization in this system as found for single-stranded DNA. The sensitization disappears with aging of the bacterial extract, but can be recovered by the addition of small amounts of a compound like cytochrome C. (no Refs)

40. PHOTOSENSITISED DEGRADATION OF DNA BY DAUNOMYCIN (MEETING ABSTRACT).

Phillips DR, Gray PJ
La Trobe University, Melbourne, Australia
Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

Daunomycin (daunorubicin, rubidomycin) and adriamycin are widely used in the treatment of cancers. The action of these drugs is due mainly to their ability to intercalate into DNA. When daunomycin-DNA complexes were irradiated with visible light, degradation of the DNA was observed by a dramatic decrease of the viscosity of the soln and by an increase of the rate of denaturation of the DNA in the presence of formaldehyde. In the absence of daunomycin, little degradation was evident. The extent of degradation increased with drug:nucleotide ratio up to 0.2, although the apparent number of binding sites on the DNA was only 0.10 at the ionic strength employed. The degradation of the DNA appeared to proceed by OH radicals (which were detected by electron spin resonance (ESR) using a spin-trapping technique) and was confirmed by the greatly reduced extent of degradation of the

DNA when the OH radical spin trap was present during visible irradiation of the DNA-drug soln. (no Refs)

41. A STUDY OF THE ORGAN DISTRIBUTION AND BINDING OF 1-METHYL-1-NITROSOUREA (MNU) AND 1-METHYL-3-NITRO-1-NITROSOGUANIDINE (MNNG) AFTER ORAL ADMINISTRATION IN THE GUINEA PIG (MEETING ABSTRACT).

Woolley PV, Yerino P
Division of Medical Oncology, Georgetown University Medical Center, Washington, DC, 20007
Newsletter Natl Pancreas Cancer Project; VI(2):67 1981

The induction of pancreatic carcinoma in the guinea pig by the oral administration of MNU is an important animal model for this disease. Much of our effort is directed at an analysis of this system and at a comparison of MNU with the related compound MNNG, which is a gastric carcinogen rather than a pancreatic carcinogen after oral administration. In this study we have compared directly the distribution of these two agents in the guinea pig. Each drug synthesized with 14C in either the methyl group or the carbonyl (guanidino) carbon and these separate preparations were given as a single oral dose of 0.1 mmoles/kg body wt. Organ uptake as a function of time was expressed as total and acid-insoluble radioactivity. Alkylation was estimated as the radioactivity in DNA, RNA and protein fractions and confirmed by measuring the formation of 7-methylguanine on high pressure liquid chromatography. Widespread distribution of these drugs was measurable. Highest levels of all 4 drug labels were found in the liver. For other organs, including the pancreas, peak whole tissue levels ranged from 10-50 nmoles/g, of which 20-30% was TCA-precipitable. In the stomach, alkylation of DNA and RNA was comparable for MNU and MNNG, but in all other organs MNU binding was 2-10 fold greater than MNNG. This difference was very evident in the pancreas. Binding of MNU in the pancreas was comparable to that in other organs and persisted at least 24 hr. The data show that the pancreas and other organs are readily modified by the oral administration of MNU. They support the idea that MNU would be a more potent pancreatic carcinogen than MNNG, in agreement with earlier data in pancreatic lobules. (no Refs)

EFFECT OF CARCINOGENS ON MACROMOLECULAR SYNTHESES

42. RAT ALPHA-FETOPROTEIN IS NOT PRODUCED CONSTITUTIVELY IN MOUSE HEPATOMA X NORMAL ADULT RAT HEPATOCYTES HYBRIDS, NOR IS IT INDUCIBLE BY ETHIONINE TREATMENT (MEETING ABSTRACT).

Szpirer J, Szpirer C
Genetic Laboratory, Free University of Brussels, Rhode-St-Genese, Belgium
Oncodev Biol Med; AbstractsBook,1:P7 1981

We have previously reported that hepatocyte hybridomas can be generated by fusing mouse hepatoma cells with hepatocytes from normal abult rat; such hybrids segregate rat chromosomes, but retain the capacity to secrete one or several rat serum proteins like the normal hepatocyte parent. They actively secrete mouse alpha fetoprotein (AFP), like the parental mouse hepatoma cells, but do not produce rat AFP in sizeable amount. We have now isolated new hybrids clones which differ from the previous ones in having retained a high number of rat chromosomes; however, like the previous hybrids, they do not secrete rat AFP in amount detectable by radioimmunoassay. No stimulation of AFP production could be observed by treating hybrid cells with ethionine, a hepatocarcinogen known to activate AFP production in vivo. In these hybrids, the rat AFP genes, contributed by the adult hepatocyte are thus not activated, although they co-exist with active mouse AFP genes. In the course of this study, we also found that rat hepatoma lines derived from the Reuber H35 hepatoma secrete low amounts of rat AFP; their rate of AFP secretion changes during the growth cycle (it is decreased during the stationary phase), and is not stimulated by ethionine treatment, or by hybridization with AFP-producing mouse hepatoma cells. (no Refs)

43. GUINEA-PIG AFP DURING NORMAL ONTOGENESIS, LIVER CARCINOGENESIS, AND UNDER HORMONE TREATMENTS (MEETING ABSTRACT).

Gourdeau H, Belanger L
Molecular Oncology Laboratory, Laval University, Quebec City, Quebec, Canada
Oncodev Biol Med; AbstractsBook,1:P6 1981

Guinea-pig alpha fetoprotein (AFP) was purified to homogeneity, characterized, and a radioimmunoassay was developed. Serum AFP level in fetal guinea-pig remains in the mg/ml range up to the 8th gestational wk and then drops rapidly. The electrophoretic and lectin affinity molecular variants of AFP change during ontogenesis, probably in relation with changes in carbohydrate composition of the protein. The liver and the yolk sac are the main sites of AFP synthesis during fetal life with the stomach and the small intestine contributing smaller amounts, as measured by peptide pulse labeling assays in vivo. Compared to other species, serum AFP levels are very high in normal adult guinea-pig; these levels are reduced dramatically by administration of glucocorticoids or ACTH. The hormone effect is rapidly reversed upon withdrawal. In guinea-pigs fed with diethylnitrosamine, serum AFP increases at the time liver tumors appear; there is no early induction and the increase is much less than in rats under similar treatme nt. (no Refs)

44. ABNORMAL GLYCOSYLATION OF AFP DURING 3'MDAB HEPATOCARCINOGENESIS (MEETING ABSTRACT).

Kelleher PC, Smith CJ, Schwartz CE, Chiu JF
Department of Medicine, University of Vermont, Burlington, VT, 05405
Oncodev Biol Med; AbstractsBook,1:36 1981

Chemically-induced hepatomas secrete alpha fetoprotein (AFP) which reacts differently with concanavalin A (ConA) than does AFP secreted by regenerating liver. We investigated binding to ConA of AFP secreted during 3'-methyl-4-dimethylaminoazobenzene (3'MDAB) hepatocarcinogenesis. 3'MDAB (0.06%) was fed continuously until either hepatomas developed or the rats were killed after predetermined time intervals between 7 and 165 days. AFP was measured immunochemically and ConA-binding characterized by affinity chromatography. Each result is the mean of 4 to 6 rats. Nineteen and 27 days after starting 3'MDAB feeding, 53 and 57% of serum AFP was ConA-nonbinding. Between 33 and 81 days the percent nonbinding AFP was stable, between 27 and 35% (6 sampling dates). Subsequently, the percentage of nonbinding AFP present at each sampling date rose to between 42 and

71%, fluctuating widely between sampling dates. Serial sampling of individual rats revealed a similar change in AFP binding to ConA during 3'MDAB feeding. Variations within animals was as great as the variation between animals. At no period of time during 3'MDAB feeding was the pattern of AFP binding to ConA similar to that during liver regeneration, indicating that the processing of AFP during hepatocarcinogenesis differs from that during liver regeneration. Altered AFP glycosylation is an early event in hepatocarcinogenesis. (no Refs)

45. DETECTION OF HYALURONECTIN OR MESENCHYM ASSOCIATED ANTIGEN IN THE EARLY STAGES OF COLONIC CARCINOGENESIS INDUCED BY 1-2 DIMETHYLHYDRAZINE (MEETING ABSTRACT).

Halkin E, Delpech B, Laumonier R, Tayot J, Delapierre F
Centre Henri Becquerel, Rue d'Amiens, 76 038 Rouen Cedex, France
Oncodev Biol Med; AbstractsBook,1:P17 1981

This study dealt with the detection of a protein 'hyaluronectin' in the colon of 1,2-Dimethylhydrazine treated rats. Hyaluronectin is a hyaluronic binding glycoprotein that is associated with fetal, reactive or cancerous mesenchyme. Immunohistochemistry study used the indirect method with an immune-serum conjugated with peroxidase. The dose dependence, the latency period of hyaluronectin production in tumors and preneoplastic lesions have been studied. It is concluded that hyaluronectin could be considered as a marker of the changes in colon tissue from the time of initiation in carcinogenesis. (no Refs)

46. INFLUENCE OF SOLE OR COMBINED TREATMENT WITH X-RAYS, QUINACRINE OR CHLOROQUINE ON GROWTH AND MELANIN FORMATION OF SERIALLY CULTURED MOUSE MELANOMA CELLS (HPM-73 LINE) (MEETING ABSTRACT).

Schachtschabel DO, Biller H, Leising HB
Institut fur Physiologische Chemie, Philipps-Universitat Marburg, D-3550 Marburg, W. Germany
Third European Workshop on Melanin Pigmentation, September 28-October 1, 1981, Prague, Czechoslovakia. Czechoslovak Medical Society 128 pp., 1981.

Exposure of Harding-Passey melanoma cells (HPM-73) in monolayer culture during exponential growth phase to a single x-ray dose of 200 or 400 Rad resulted in retardation (up to 3 days) followed by resumption of cell proliferation. Eight hundred Rad (or higher doses) caused a significant reduction of survival rate. This growth-inhibitory effect was augmented by continuous incubation in the presence of quinacrine (atebrine) or chloroquine (resochine) at concentrations which alone were slightly or not inhibitory. Combinations of 800 Rad and 6 x 10-6M quinacrine or chloroquine resulted in death of all cells. The specific melanin content (E400/mg cell protein) of cultures treated (6 days) with quinacrine alone was not affected, while irradiation or exposure to chloroquine alone led to a moderate increase (up to 50%). A more pronounced elevation was reached by combined treatment with x-rays and quinacrine or chloroquine. The effects of quinacrine and chloroquine on x-ray irradiated cells might be related to their DNA repair inhibiting properties. (no Refs)

47. THE EFFECT OF 5-(3,3-DIMETHYL-1-TRIAZENO)-IMIDAZOLE-4-CARBOXAMIDE AND X-RADIATION ON MAMMALIAN CELLS IN CULTURE.

Nagy B, Bistrovic M, Maricic Z
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Libri Oncol; 10(1):53-57 1981

The interaction of 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide (DTIC) and x ray irradiation was studied by combined treatment on survival of cells in culture, and on cell macromolecules synthesis. Clone cell line L929 originating from mouse fibroblasts was used in cell cultures. DTIC was prepared immediately before, used in 0-1,500 ug/ml concentrations for 3 hr. The cell survival gave a sigmoid curve. DNA synthesis was decreased in DTIC treated cells. In combined treatment, 500 ug/ml DTIC was used, after varying amounts of irradiation. DTIC effect on cell survival time, could be detected with greater than 500 radiation absorbed dose (rad). DTIC decreased DNA synthesis approx 30% after prolongued incubation, but after 3 hr incubation this effect cannot be detected, although survival time at that point is decreased 60%. DTIC apparently attacked other vital processes, before its effect on DNA could be observed. Irradiation decreases DNA synthesis. Addition of DTIC did not enhance that decrease. (14 Refs) (In SCR)

48. METABOLIC ACTIVATION IN TYPE II ALVEOLAR LUNG CELLS OF THE RAT WITH EXPOSURE TO BENZO(A)PYRENE (MEETING ABSTRACT).

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School of Medicine, Department of Physiology and Pharmacology, Loma Linda Univer sity, Loma Linda, CA, 92350
In Vitro; 17(3):201 1981

L-2 cells clonally derived from adult rat lungs with characteristics of type II pneumonocytes exhibited elevated aryl hydroxylase (AHH) and epoxide hydratase (EH) activity following exposure to benzo(a)pyrene [B(a)P]. Max AHH activity was measured fluorometrically at 24 hr and increased linearly over this time period. Peak AHH activity was 10 x that of basal levels while peak EH activity was about twice basal levels. Nuclear AHH activity was 10 percent that of the whole cells. Theophylline inhibited AHH activity and binding of tritium-labeled metabolites to nuclear macromolecules whereas the prostaglandin synthetase inhibitors indomethacin and sodium meclofenamate stimulated AHH activity and binding of labeled metabolities to nuclear macromolecules. Both the organic and water soluble metabolites extracted from the culture medium failed to produce mutagenesis in four strains of Salmonella typhymurium and in Chinese hamster V-79 cells. Unscheduled DNA synthesis was not observed in L-2 cells exposed to B(a)P. These results suggest that the enzyme activation and subsequent metabolism of benzo(a)pyrene in L-2 cells yields nonmutagenic and noncarcinogenic products and if representative may offer a partial explanation for the low incidence of type II cell involvement in human lung cancer. (1 Ref)

49. THE MAJOR ADDUCTS OF CIS AND TRANS BENZO[A]PYRENE DIOL EPOXIDES CAUSE CHAIN TERMINATION DURING DNA SYNTHESIS IN VITRO.

Yamaura I, Rosenberg BH, Cavalieri LF
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Chem Biol Interact; 37(1):171-180 1981

We have studied DNA synthesis in vitro using as template phiX174 DNA containing varying numbers of adducts formed by reaction with cis and trans benzo[a]pyrene (BP) diol-epoxides. The extent of DNA synthesis decreases with increasing numbers of adducts and there is a concomitant decrease in the size of the DNA products. Both decreases can be accounted for quantitatively by the assumption that synthesis terminates at every BP adduct. Since the majority of the adducts are located at the 2-amino group of guanine, we deduce that these adducts cause termination. The role of adducts at other sites is uncertain. The cis and trans BP diol-epoxides are indistinguishable with regard to chain termination, yet in vivo these isomers behave differently. These results suggest that chain determination alone is insufficient to account for the mutagenic effects of BP diol-epoxides. (Author abstract) (26 Refs)

REVIEWS

50. EPOXIDE HYDROLASE AND HEPATOCARCINOGENESIS.

Griffin MJ
Oklahoma Medical Res. Foundation, 825 N.E. 13th St., Oklahoma City, OK, 73104
Trends Pharmacol Sci; 2(10):257-258 1981

The role of epoxide hydrolase (EH) in hepatocarcinogenesis is described. A search for markers associated with multistage development of preneoplastic cells through focal and nodular stages to a hepatoma led to the discovery of the preneoplastic (PN) antigen, a microsomal antigen present in nodule and hepatoma cells. Through immunological studies EH was found to be a major PN antigen. A class of heterocyclics, including isoquinoline, norharman, and ellipticine, has been shown to stimulate microsomal EH. The requirement for a pyridinic nitrogen beta to a ring fusion suggests enzyme dictated specificity, while the pyridinic nitrogen suggests an electrophilic target. Reactive electrophiles, such as epoxides, have been found to regulate cell function and development. Perhaps endogenously formed epoxides play a role in liver adaptation during hepatocarcinogenesis. All hepatocarcinogen tests seem to cause an early (1-5 wk) induction of EH activity and microsomal content of the enzyme protein. One explanation for this early induction of EH is the production of increased amounts of an endogenous epoxide as an acute response. EH regulation during hepatocarcinogenesis is discussed with 2-acetylaminofluorene hepatocarcinogenesis as an example. (12 Refs)

51. SOME GENETIC ASPECTS OF CANCER.

Bernstein R
Dept. Human Genetics, Sch. Pathology, Univ. Witwatersrand, Johannesburg, South Africa
S Afr Cancer Bull; 25(3):147-153 1981

Some of the genetic factors interacting with environmental mutagens in the etiology of cancer, are discussed under the headings of (1) inherent chromosome imbalance and (2) single gene mutations. These single gene disorders may be due to (a) defects in DNA replication and/or repair pathways causing cellular instability or (b) defects in immune surveillance mechanisms for protecting the cell. These genetic factors are correlated with the visible chromosomal markers of malignant or potentially malignant cells. (Author abstract) (38 Refs)

52. CARCINOGEN BINDING TO DNA.

Straub KM, Burlingame AL
Dept. Pharmaceutical Chemistry, Univ. California, San Francisco, CA, 94143
Biomed Mass Spectrom; 8(9):431-435 1981

Analytical methods currently in use for the structural identification of different types of carcinogen DNA adducts and future trends in mass spectrometry are presented. Application of mass spectrometry to identification of nucleotide structures is limited due to the highly polar, thermally labile nucleotide character. Chemical derivatization is traditionally utilized to increase the volatility of a sample. However, this procedure is difficult on a sub-ug scale and significant alteration of original structure can lead to artifacts. These problems have led to research into novel ionization techniques. Field desorption (FD) mass spectrometry avoids the need for chemical derivatization, resulting in a decreased sample requirement. Such improvement in sensitivity may allow for direct analysis of carcinogen adducts obtained from in vivo experiments. Utilizing this procedure for definitive stereochemical assignments (essential to interpreting structure-activity correlations of carcinogens) is virtually impossible due to nucleic alkylation. Information provided by FD spectra, fragmentation patterns, and NMR could permit stereochemical assignment. Future developments in mass spectrometry will allow for identification of carcinogen adducts at levels between 1-10 nanog. Future applications could include, for example, detection of carcinogen adducts in the urine of individuals who have been exposed to carcinogens. (9 Refs)

53. STRUCTURAL ASPECTS OF CHEMICAL CARCINOGENESIS (MEETING ABSTRACT).

Glusker JP
Institute for Cancer Research, 7701 Burholme Avenue, Philadelphia, PA, 19111
Molecular Structure and Biological Activity: A Symposium on Biologically Active Molecules, (Twelfth Congress), August 26-28, 1981, Buffalo, New York. International Union of Crystallography 89 pp., 1981.

The process of carcinogenesis by polycyclic aromatic hydrocarbons (PAH) involves the enzymatic 'activation' of the hydrocarbon to a diol epoxide and, it is presently believed, alkylation of DNA by this alkylating agent. The shape and size of the PAH is important. If it is too large or too small it is not as potent a carcinogen. The optimal size approaches that of a steroid or a base pair. This shape may also have significance in the interaction of the PAH with the hydroxylating enzyme. In addition, methyl substitution for hydrogen in the 'bay area' of a PAH, which characteristically causes distortions as a result of steric effects, often enhances carcinogenic activity. Studies in several systems have led to the conclusion that flatness is not a criterion for carcinogenicity and that total intercalation of the hydrocarbon cannot occur. The benzoflavone that inhibits the 'activation' process has been shown by x-ray studies to be nonplanar. Interactions between hydroxyl and epoxide groups in the same molecule may affect reactivity. The immediate aim of these studies is to determine what effects alkylation by an activated PAH can have on DNA. The structure of a nucleoside alkylated by chloromethyl PAH has been studied and it is

shown, as predicted, that the base and PAH portion lie almost perpendicular to each other. Some possible effects of such alkylation on DNA structure will be discussed. (no Refs)

54. ADVANCES IN THE METABOLIC ACTIVATION OF CARCINOGENS.

Ivanetich KM
Dept. Medical Biochemistry, Univ. Cape Town Medical Sch., Observatory, Cape Province, South Africa
S Afr Cancer Bull; 25(1/2):105-116 1981

Of the known chemical carcinogens, an ever-increasing number require metabolic activation to elicit their mutagenic and carcinogenic effects. In a review, it is noted that the enzymes kn own as cytochrome P-450 alone or in conjunction with other enzymes are involved in this activation. The activated metabolites may initiate carcinogenesis by covalently binding to selected sites on nuclear DNA in somatic cells. Detailed pathways are presented for a number of carcinogens, such as chlorinated ethylenes, aflatoxin B1, acetylaminofluorene and benzpyrene. (22 Refs)

55. MEMBRANE CHOLESTEROL, TUMORIGENESIS, AND THE BIOCHEMICAL PHENOTYPE OF NEOPLASIA.

Coleman PS, Lavietes BB
Lab. Biochemistry, Dept. Biology, New York Univ., New York, NY
CRC Crit Rev Biochem; 11(4):341-393 1981

Arguments are given for the proposal that abnormalities in the biosynthetic regulation of lipids, particularly cholesterol, constitute early events in tumorigenesis and underlie many of the phenotypic hallmarks of malignant neoplasia. Information on the cholesterol molecule is presented and its proposed role as a lipid component of biological membranes is discussed. Some features of regulated cholesterol synthesis in normal vs neoplastic cells are highlighted; evidence that proliferating cells have a special requirement for sterol synthesis is documented. Views on the way in which aberrant regulation of cholesterol biosynthesis occurring early in tumorigenesis can lead directly to other documented characteristics of tumor cell metabolism, particularly those aspects concerning cellular respiration, are presented. The cancer-stricken host, in whom plasma membrane fragments are shed from the tumor as microvesicles containing tumor antigenic determinants, is considered. (300 Refs)

56. ASSESSMENT OF THE ROLE OF MUTAGENS AND ENDOGENOUS FACTORS IN LARGE BOWEL CANCER.

Weisburger JH, Spingarn NE, Wang YY, Vuolo LL
American Health Foundation, Valhalla, NY
Cancer Bull; 33(4):124-129 1981

Etiology of large bowel cancer is discussed. The production of abnormal DNA through the direct attack of radiation, chemicals, or viruses, or through improper DNA polymerase activity during DNA synthesis or repair, is only the first step in a long sequence of events terminating in a malignant invasive neoplasm. Rate of cell duplication as controlled by promoters or inhibitors is also important for neoplasm development. Chemical carcinogens, accounting for the majority of human cancers, can be divided into two major groups: genotoxic (direct-acting, procarcinogen, and inorganic carcinogen) and epigenetic (solid-state carcinogen, hormone, immunosuppressor, co-carcinogen, and promoter). Colon cancer incidence and mortality vary as a function of geographic area of residence. The key environmental difference between low-risk and high-risk countries appears related to diet, particulary fat and fiber consumption. In order for colon cancer to occur, both promoters (ie high fat diet) and initiators (ie mutagens produced during fr ying or broiling of meats and fish) may be required. Variations in these factors and high fiber intake can alter the incidence of colon cancer. (38 Refs)

57. DISTINCT REGULATORY CONSEQUENCES REQUIRED FOR GENOTOXIC CARCINOGENS AND PROMOTING AGENTS (MEETING ABSTRACT).

Weisburger JH, Williams GM
American Health Foundation, Valhalla, NY
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

We have classified chemical carcinogens into two broad classes, genotoxic and epigenetic carcinogens, subdivided in turn into eight subclasses. The mechanisms of each subclass need to be established in detail to provide the basis for rational regulatory actions applied to protect man effectively, efficiently, and economically. Genotoxic carcinogens are generally conceived to be electrophilic compounds reacting with critical cellular macromolecules, especially DNA. Unless such DNA is competently repaired, the damage can be converted into an irreversible mutation during replication. Multiplication of cells with such abnormal DNA leads to progeny bearing the neoplastic genome which can, through further infidelity in DNA synthesis, progress to more advanced neoplastic states. Conceptually, therefore, the effect of genotoxic carcinogens leads to irreversible changes, even though dose response curves do seem to indicate the existence of a practical, albeit not theoretical, thresholds. Epigenetic carcinogens operate by diverse mechanisms, sometimes highly specific as regards species, strain and tissue activity. In many instances, one mode of action is the control of the rate of cell multiplication through mechanisms to be established further. This action is highly dose dependent and is reversible. Thus, there is a time and dose threshold for such substances. Evidently, regulatory stances for such compounds should be quite different from those applicable to genotoxic carcinogens. We have devised a systematic sequence of tests to distinguish between these two major categories of carcinogens, which, when used properly, yields a data base appropriate for scientifically sound regulatory actions. (no Refs)

58. AIR POLLUTION AND BIOLOGICAL DEFENCE.

Schlipkoter HW, Dolgner R
Med. Institut fur Umwelthygiene an der Univ., Gurlittstrasse 53, D-4000 Dusseldorf 1, W. Germany
Zentralbl Bakteriol [Orig A]; 172(4/5):299-311 1981

A review is presented of the effects of air pollution on defense mechanisms of the body which may in turn account for differences in individual reactivity to such pollution. Some important findings relating to this problem follow: deterioration of lung clearance after inhalation of NO2 and lead chloride; damage to alveolar macrophages by air-borne particulates in vitro and in vivo; enhanced activation of C3 complement fraction under the influence of air pollutants; higher frequency of enlarged tonsils and lymph nodes, of pathogenic bacteria on tonsillar surfaces, and of relatively lower lysozyme concentrations in children living in urban or industrialized areas; decreased resistance to infections related to inhalation of O3 or a lead aerosol; immuno-suppressive effect of heavy metals and organic compounds; allergic reactions to many chemicals; detoxification and toxification, eg formation of ultimate carcinogens, and of organic molecules; induction or inhibition of

benzo(a)pyrene metabolism by particulate extracts or by CO, NO2, and lead; deficiency of DNA-repair in disease conditions predisposing to development of cancer; tendency, in allergic subjects, to a relatively lower incidence of cancer; adaptation to the effect of CO and SO2. These facts, and others not cited, support a close connection between various defense mechanism, air pollution, and its effects on the human organism. (55 Refs) (In GER)

59. INTERFACE BETWEEN CELL BIOLOGY AND CHEMOTHERAPY.

Allfrey VG
Rockefeller Univ., New York, NY
Cancer Bull; 33(4):129-135 1981

Developments in cell biology affecting the understanding and treatment of cancer are discussed. New techniques useful in cancer research include the creation of hybrid cells by fusion of their plasma membranes, microinjection techniques, discovery of DNA-mediated gene transfer, DNA cloning and sequencing, techniques that have simplified cell-cycle analysis, cell sorting, and isolation of particular cell types, and new techniques for the analysis of DNA structure employing restriction endonucleases. Many of the new approaches offer the prospect of more incisive analysis of early events in tumor initiation and progression. Areas of cell biology using these techniques are discussed, including those with relevance to carcinogen damage, mechanisms of transcriptional control, cell-cycle progression in malignant cells, and modulation or suppression of the malignant phenotype. Implications of these findings for cancer chemotherapy are outlined. Chemotherapy aimed at selective inhibition of tumor DNA and protein synthesis, the use of monoclonal antibody techniques in chemotherapy, and the use of magnetic albumin microspheres in tumor treatment are reviewed. (86 Refs)

60. THE ROLE OF CHROMOSOME ABERRATIONS IN HUMAN CANCER (MEETING ABSTRACT).

Bishun N
No affiliation given, Marie Curie Memorial Foundation, Oxted, England
Teach-In on Research Methods in Cancer, June 30, 1981, London, England Marie Curie Memorial Foundation; 1981

Nuerous attempts to elucidate the role of chromosomal changes in carcinogenesis have been made recently and this has been due mainly to the improvement of cytological techniques. The involvement of chromosomes in neoplastic growth, is a natural outcome of Boveri hypothesis which suggested in a more definite form that malignancy was due to an abnormal chromosome content of the cells. The reputed Boveri's Chromosome theory of cancer, suggests that chromosomal aberration is the common pathway through which carcinogenic factors induce cancer. Certain types of cancer, especially the leukemias, are known to occur with a higher frequency in Down's syndrome, in patients with sex chromosome anomalies and in their relatives. The anomalies may predispose these patients directly or indirectly to cancer and, furthermore, is not restricted only to patients with Down's syndrome or sex chromosmoe abnormalities. Certain diseases, considered to be preleukemic conditions, in addition to being carried by a recessive gene, show congenital chromosomal damage and finally develop into leukemia. In another inherited disease, Xeroderma Pigmentosa, the chromosomal aberrations present may be asynchrony of a particular chromosome during the mitotic cycle and could lead to aneuploidy and subsequent malignant transformation. Chromosomal studies and evaluation of mutagenic potential of all new and established drugs, food additives and environmental chemicals should be integral aspects of the current practices of safety evaluation of these substances, and the same stringent principles should be applied to the numerous chemicals used as solvents and intermediates in industrial processes. Persons exposed to high risk, such as those working in chemical industries, must be monitored constantly using all the methodologies at hand. (no Refs)

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Calabrese EJ

Environmental Health Program, Div. Public Health, Univ. Massachusetts, Amherst, MA

Nutrition and Environmental Health: The Influence of Nutritional Status on Pollutant Toxicity and Carcinogenicity. Volume 2: Minerals and Macronutrients. New York, John Wiley and Sons, 468 pp., 1981.

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

2. RETROSPECT AND PROSPECT OF STUDIES ON DIGESTIVE SYSTEM DISEASES IN CHINA.

Zhang X

Dept. Internal Medicine, Capital Hosp., Chinese Acad. Medical Sciences, Beijing, People's Republic of China

Zhonghua Xiaohua Zazhi; 1(1):1-4 1981

In CHI

3. EPIDEMIOLOGY OF PITUITARY ADENOMAS.

Gold EB

Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 Wolfe St., Baltimore, MD, 21205

Epidemiol Rev; 3:163-183 1981

4. BLADDER CANCER EPIDEMIOLOGY.

Matanoski GM, Elliott EA

Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 North Wolfe St., Baltimore, MD, 21205

Epidemiol Rev; 3:203-229 1981

5. THE EPIDEMIOLOGY OF BENIGN BREAST DISEASE.

Ernster VL

Dept. Epidemiology and International Health, 16/9HSW, Univ. California, San Francisco, CA, 94143

Epidemiol Rev; 3:184-202 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

6. AIR POLLUTION AND BIOLOGICAL DEFENCE.

Schlipkoter HW, Dolgner R

Med. Institut fur Umwelthygiene an der Univ., Gurlittstrasse 53, D-4000 Dusseldorf 1, W. Germany

Zentralbl Bakteriol [Orig A]; 172(4/5):299-311 1981

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7. CANCER AND THE PHYSICOCHEMICAL QUALITY OF DRINKING WATER IN QUEBEC.

Thouez JP, Beauchamp Y, Simard A

Dept. Geography, Univ. Montreal, Montreal, Quebec, Canada

Soc Sci Med [Med Geogr]; 15(1):213-223 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

8. ONCOGENIC VIRUSES.

Wyke JA

Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England

J Pathol; 135(1):39-85 1981

9. ROLE OF VIRUSES IN THE ETIOLOGY OF NATURALLY OCCURRING FELINE LEUKEMIA.

Essex M, Grant CK, Cotter SM, Hardy Jr WD

Dept. Microbiology, Harvard Sch. Public Health, 665 Huntington Ave., Boston, MA, 02115

Haematol Blood Transfus; 26:483-487 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

10. MAMMALIAN IN VIVO AND IN VITRO CYTOGENETIC ASAYS: A REPORT OF THE U.S. EPA'S GENE-TOX PROGRAM.

Preston RJ, Au W, Bender MA, Brewen JG, Carrano AV, Heddle JA, McFee AF, Wolff S, Wassom JS

Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830

Mutat Res; 87(2):143-188 1981

11. BACTERIAL SYSTEMS FOR CARCINOGENICITY TESTING.

Mohn GR

Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Wassenaarseweg 72, 2333 AL Leiden, The Netherlands

Mutat Res; 87(2):191-210 1981

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Bradley MO, Bhuyan B, Francis MC, Langenbach R, Peterson A, Huberman E

Merck Inst. for Therapeutic Res., West Point, PA, 19486

Mutat Res; 87(2):81-142 1981

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13. CANCER BIOLOGY.

Ruddon RW

Biological Markers Program, NCI-Frederick Cancer Res. Center, Frederick, MD

Cancer Biology. New York, Oxford University Press, 344 pp., 1981.

14. AVOIDABLE CANCER: ATTRIBUTION OF RISK.

Doll R

Radcliffe Infirmary, Oxford, England

S Afr Cancer Bull; 25(3):125-146 1981

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BIOLOGICAL ASPECTS OF DNA ALTERATION AND REPAIR IN RELATION TO CARCINOGENICITY

1. ABNORMAL REGULATION OF DNA REPLICATION AND INCREASED LETHALITY IN ATAXIA TELANGIECTASIA CELLS EXPOSED TO CARCINOGENIC AGENTS.

Jaspers NG, De Wit J, Regulski MR, Bootsma D
Dept. Cell Biology and Genetics, Erasmus Univ. Rotterdam, Post Office Box 1738, 3000 DR Rotterdam, The Netherlands
Cancer Res; 42(1):335-341 1982

The effect of different carcinogenic agents on the rate of semiconservative DNA replication in normal human and ataxia telangiectasia (AT) cells was investigated. The rate of DNA synthesis in all AT cell strains tested was depressed to a significantly lesser extent than in normal cells after exposure to x-rays under oxia or hypoxia or to bleomycin, agents to which AT cells are hypersensitive. In contrast, inhibition of DNA replication in normal human and AT cells was similar after treatment with some DNA-methylating agents or mitomycin C. Colony-forming ability of AT cells treated with these agents was not different from normal cells. Treatment with 4-nitroquinoline 1-oxide elicited a variable response in both AT and normal cell strains. In some strains, including those shown to be hypersensitive to the drug by other workers, the inhibition of DNA synthesis was more pronounced than in other cell strains, but no significant difference between AT and normal cells could be detected. The rejoining of DNA strand breaks induced by x-rays, measured by DNA elution techniques, occurred within 2 hr after treatment and could not be correlated with the difference in DNA synthesis inhibition in AT and normal cells. After low doses of x-rays, AT cells rejoined single-strand breaks slightly more slowly than did normal cells. The rate of DNA replication in x-irradiated AT and normal cells was not affected by nicotinamide, an inhibitor of poly(adenosine diphosphate ribose) synthesis. These data indicate that the diminished inhibition of DNA replication in carcinogen-treated AT cells (a) is a general characteristic of all AT cell strains, (b) correlates with AT cellular hypersensitivity, (c) is not directly caused by the bulk of the DNA strand breaks produced by carcinogenic agents, and (d) is not based on differences in the induction of poly(adenosine diphosphate ribose) synthesis between x-irradiated AT and normal cells. (Author abstract) (47 Refs)

2. RADIORESISTANT DNA SYNTHESIS: AN INTRINSIC FEATURE OF ATAXIA TELANGIECTASIA.

Painter RB
Lab. Radiobiology, Univ. California, San Francisco, CA, 94143
Mutat Res; 84(1):183-190 1981

Radioresistance of DNA synthesis (DNAS) was compared in normal human diploid cells of cell line HS27 and six strains derived from patients with ataxia telangiectasia (AT). Three of the AT cell lines had previously been classified as proficient in repair replication after gamma-irradiation. Inhibition of DNAS was measured by incorporation of 14C-thymidine. Cells of normal and AT lines were exposed to 0-5,000 rads of x-rays. To determine the rate of DNAS at various times after irradiation, cultures were pulse-labeled at various times after irradiation. DNAS was strongly inhibited by up to 1,000 rads in HS27, but not in AT cells. DNAS was inhibited to a lesser extent between 1,000 and 5,000 rads in both HS27 and AT cells. In HS27 cells DNAS was reduced to approx 35% of control values for 1 hr, increasing to 60% from 2 to 4 hr after irradiation. In AT cells DNAS was reduced to 75-80% of control values 90 min after irradiation and remained at that level after 4 hr. Inhibition of replicon initiation was the primary factor in radioresistance of AT cells. Chain elongation was also more radioresistant in AT cells than in HS27 cells. Up to 2,000 rads inhibition of DNAS in AT cells was due almost entirely to inhibition of replicon initiation and not of chain elongation. (17 Refs)

3. CHROMOSOMAL DAMAGE INDUCED BY FUROCOUMARINS AND UVA IN HAMSTER AND HUMAN CELLS INCLUDING CELLS FROM PATIENTS WITH ATAXIA TELANGIECTASIA AND XERODERMA PIGMENTOSUM.

Natarajan AT, Verdegaal-Immerzeel EA, Ashwood-Smith MJ, Poulton GA
Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Wassenaarseweg 72, 2333 AL Leiden, The Netherlands
Mutat Res; 84(1):113-124 1981

The relative capacities of four furocoumarins to sensitize cells to near-UV (UVA) were studied in Chinese hamster ovary cells (CHO) and human cells from normal, ataxia telangiectasia (AT), and xeroderma pigmentosum (XP) individuals. Cells were exposed in vitro to psoralen (PS), 5-methoxypsoralen (5MOP), 8-methoxypsoralen (8MOP), or angelicin (AN) at concentrations of 40 ug/ml. Cultures were irradiated with UVA (320-380 nanometers). In CHO cells the most active substance was PS, followed in order by 8MOP, 5MOP, and AN. The first three produced DNA monoadducts and cross-links, but AN produced only adducts. All four compounds produced higher rates of sister chromatid exchanges (SCE) in AT and XP cells than in normal human cells. AN required high UVA doses to produce damage compared with 8MOP and 5MOP. Normal human cells were approx 2.3 times as sensitive to SCE production than CHO cells. Damage was of the type produced by UV or alkylating agents. Results indicate that 5MOP produces the same effects in human cells as the known carcinogen 8MOP. The use of 5MOP in suntan preparations should therefore not be permitted. (22 Refs)

4. A UV-SENSITIVE HUMAN CLONAL CELL LINE, RSA, WHICH HAS LOW REPAIR CAPACITY.

Suzuki N, Fuse A
Dept. Microbiology, Chibe Univ. Sch. Medicine, Inohana, Chiba 280, Japan
Mutat Res; 84(1):133-145 1981

DNA repair activity, as measured by incorporation of [methyl-3H]thymidine ([3H]dThd) or 5-[6-3H]bromodeoxyuridine ([3H]BrdUrd) was compared in human transformed cell line RSa and HeLa cells. RSa cells were derived by double infection with Rous sarcoma virus and Simian virus 40. Cell cultures were exposed to UV radiation (0.8 Joules/square meter/sec for up to 2 min) or mock irradiation. Assay of cell survival and colony formation indicated that RSa cells were much more sensitive to UV than HeLa cells. Unscheduled DNA synthesis (UDS) was measured after treatment with hydroxyurea or with arginine deprivation to reduce scheduled DNA synthesis. RSa cells showed less than half the UDS of HeLa cells. Assay of repair replication by recentrifugation of isolated parental DNA showed lower rates in RSa than in HeLa cells. Results indicate that excision repair in RSa cells is abnormally low. The mechanism of UV sensitivity and reduced DNA repair is unknown. (48 Refs)

BIOLOGICAL ASPECTS OF DNA ALTERATION AND REPAIR IN RELATION TO MUTAGENICITY

5. MUTAGENESIS AND TRANSFORMATION OF C3H 10T 1/2 CELLS TREATED WITH ETHYL METHANESULFONATE.

Evans HH, Wilkins L, Horng MF, Santoro C, Evans TE, Glazier KG
Div. Radiation Biology, Dept. Radiology, Case Western Reserve Univ., Cleveland, OH, 44106
Mutat Res; 84(1):203-219 1981

The effects of ethyl methanesulfonate (EMS) on survival (plating efficiency: PE), mutagenesis (induction of ouabain resistance), and transformation (induction of altered colony morphology on monolayers or of colony formation in semi-solid media) were studied. Cell lines used included mouse embryo-derived C3H 10T1/2 (clone 8), the chemically transformed counterpart MCA, BALB 3T3, and virally transformed SVT2. Cell monolayers were treated with various concentrations of EMS for 2 hr. Incubation of confluent monolayers for 4 hr following EMS exposure allowed some excision repair of DNA to occur and resulted in increased survival, transformation, and mutation. Extension of the repair period to 24 hr allowed further DNA repair to occur and resulted in lower rates of transformation and mutation than after 4-hr incubation. The PE of one ouabain-resistant (Oua-R) strain increased as the density of ouabain-sensitive (Oua-S) cells increased. In other Oua-R strains PE was reduced when Oua-S density increased over 1 x 10(3) cells/square cm. Results indicate that the length of DNA repair periods affects the frequencies of mutation and transformation. (61 Refs)

6. BASE-PAIR SUBSTITUTION HOTSPOTS IN GAG AND GCG NUCLEOTIDE SEQUENCES IN ESCHERICHIA COLI K-12 INDUCED BY CIS-DIAMMINEDICHLOROPLATINUM (II).

Brouwer J, Van de Putte P, Fichtinger-Schepman AM, Reedijk J
Lab. Molecular Genetics, State Univ. Leiden, Wassenaarseweg 64, 2333 AL Leiden, The Netherlands
Proc Natl Acad Sci USA; 78(11,part2):7010-7014 1981

Cell killing and mutation induction by cis- and trans-PT(NH3)2CL2 in Escherichia coli were examined by studying forward mutagenesis in the lacI gene in cells with different repair capacities. Survival experiments showed that repair-proficient cells were slightly more sensitive for the cis isomer than for the trans isomer, whereas repair-deficient RecA and UvrB cells were extremely sensitive only for the cis compound. cis-Pt(NH3)2Cl2 induced mutagenesis in both wild-type cells and RecA cells but not in UvrB cells; whereas no detectable mutagenesis was induced by treatment with the trans compound. Examination of the nature of the mutations induced by cis-PT(NH3)2Cl2, by using the LacI system, revealed that ba sepair substitutions leading to nonsense mutants are only induced in wild-type cells, suggesting that the intact products of both the uvrB and the recA gene are necessary for the repair responsible for this type of mutagenesis. Investigation of the nonsense mutants reveals that 70% of these mutations result from GC - TA or GC - AT substitutions at sites where the guanine is part of a GAG or GCG sequence. These results are discussed in relation to existing theories on the interaction between Pt compounds and DNA. A model for Pt-DNA adducts, leading to base-pair substitutions, is proposed. (Author abstract) (50 Refs)

7. MUTAGENIC EFFECT OF FUROCOUMARIN MONOADDUCTS AND CROSS-LINKS ON BACTERIOPHAGE LAMBDA.

Belcgurov AA, Zavilgelsky GB
Inst. Molecular Biology, Acad. Sciences USSR, Moscow, USSR
Mutat Res; 84(1):11-15 1981

The effects of 8-methoxypsoralen and light on bacteriophage lambda were studied. Escherichia coli bacteria were used as hosts. After one irradiation the primary products were monoadducts in DNA. Repeated irradiations formed only cross-links, which had a higher mutagenic effect than monoadducts. Inactivation of bacteriophage occurred only after multiple irradiations. (14 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN VERTEBRATES

8. DIFFERENT ACTIVITIES OF UNSCHEDULED DNA SYNTHESIS IN HUMAN MELANOMA AND BONE MARROW CELLS.

Lewensohn R, Ringborg U, Hansson J
Radiumhemmet, Karolinska Hosp., S-104 01 Stockholm, Sweden
Cancer Res; 42(1):84-88 1982

Unscheduled DNA synthesis (UDS) induced by melphalan was studied in freshly collected tumor cells from human melanoma metastases. Comparative studies were done on human bone marrow blast cells. Significant levels of UDS comparable with those in myeloblasts were found in only two of eight melanoma cell populations. This difference between melanoma and blast cells was not related to differential cellular uptake of melphalan. When UDS was induced by UV irradiation, significant levels of UDS were found in all melanoma and blast cell populations studied. Also, in a human melanoma cell line, high levels of UDS were found after exposure to UV irradiation, while treatment with melphalan did not result in detectable levels of UDS. Possible explanations for the divergent results of UDS in melphalan-exposed melanoma cells are discussed. (Author abstract) (23 Refs)

9. THE IN VIVO FORMATION AND REPAIR OF DNA ADDUCTS FROM 1'-HYDROXYSAFROLE.

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Dept. Biological Sciences, Stanford Univ., Stanford, CA, 94305
J Supramol Struct Cell Biochem; 16(1):83-90 1981

Characterization of DNA adducts formed in mouse liver in vivo by metabolically activated 1-hydroxysafrole (1-HS) and the response of human cells in vitro to DNA damage by 1'-acetoxysafro le (1-AOS) are reported. Female CD-1 mice received 12 umole (2',3'-3H)1-HS ip and were killed after 23 hr. DNA was obtained from liver cells and compared with synthetic adducts formed by reacting deoxynucleosides with electrophilic derivatives of 1-HS. Four adducts were identified, which were derived from an ester of 1-AOS. Three of the adducts were deoxyguanosine derivatives with substitution of the 2-amino group. The major synthetic adduct of deoxyguanylic acid was identified by its nuclear magnetic resonance (NMR) spectrum as N2-(trans-isosafrol-3'-yl)-deoxyguanosine. The major synthetic adduct of deoxyadenosine was identified by NMR spectrum as N6-(trans-isosafrol-3'-yl)-deoxyadenosine. Cells from the human glioblastoma cell line T98G were ex-

posed to 1-AOS after labeling of DNA with 14C-thymidine. DNA repair after exposure to 1mM 1-AOS occurred at approx 15% of the level produced after exposure to a repair-saturating dose of UV. The repair patch size after 1-AOS exposure (24 nucleotides) was similar to short-patch repair after UV exposure (30 nucleotides). (24 Refs)

10. UNSCHEDULED DNA SYNTHESIS IN NORMAL HUMAN SKIN AFTER SINGLE AND COMBINED DOSES OF UV-A, UV-B AND UV-A WITH METHOXSALEN (PUVA).

Honigsmann H, Jaenicke KF, Brenner W, Rauschmeier W, Parrish JA
Dept. Dermatology, Univ. Vienna, Aberstr. 4, A-1090 Vienna, Austria
Br J Dermatol; 105(5):491-501 1981

The aim of this study was to measure unscheduled DNA synthesis (UDS) by autoradiography in normal human skin (1) after high dose UV-A, (2) after low dose UV-A applied before or after erythemogenic doses of UV-B, (3) after high dose PUVA and (4) after therapeutic doses of PUVA applied before and after erythemogenic doses of UV-B. Single high dose UV-A exposure induced roughly 60% of the amount of UDS induced by equally erythemogenic doses of UV-B. Single low dose UV-A exposure did not induce UDS, nor did it significantly alter the amount of UV-B induced UDS when combined with UV-B exposure. Single high dose PUVA did not lead to UDS and had no influence on UV-B induced UDS when combined with UV-B exposure. Our findings indicate: (1) erythemogenic doses of UV-A induce a considerable DNA excision repair; (2) low dose UV-A neither augments UV-B induced DNA repair nor does it inhibit the repair process; (3) no UDS was shown to occur after either high or therapeutic doses of PUVA. This was unexpected since psoralen-DNA monoadducts have been shown to be repairable by a mechanism similar to excision repair of pyrimidine dimers. It is therefore assumed that PUVA as performed for therapeutic purposes either preferentially induced interstrand crosslinks not repairable via the classical repair mechanism or the repair of monoadducts was below resolution in this study; (4) therapeutic PUVA doses apparently do not interfere with excision repair of UV-B induced DNA lesions. (Author abstract) (36 Refs)

11. USE OF ANTI-DNA ANTIBODIES FOR DETECTION OF DNA RADIATION DAMAGE IN NUCLEI OF BONE MARROW CELLS OF IRRADIATED ANIMALS.

Mitriaeva NA, Moskalenko IP
Res. Inst. Medical Radiology, Kharkov, USSR
Vopr Med Khim; 27(5):676-679 1981

The applicability of immunochemical methods for detection of DNA radiation damage was evaluated in albino rats. The animals were irradiated with 25.8-258 mCi/kg, and bone marrow smears were treated with gammaglobulin from rabbits immunized with single-stranded DNA. The number of fluorescent bone marrow cells depended upon the dose of radiation and the time after irradiation. (19 Refs) (In RUS)

12. CONTRIBUTION OF INCORPORATED 5-BROMODEOXYURIDINE IN DNA TO THE FREQUENCIES OF SISTER-CHROMATID EXCHANGES INDUCED BY INHIBITORS OF POLY-(ADP-RIBOSE)-POLYMERASE.

Natarajan AT, Csukas I, Van Zeeland AA
Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Sylvius Lab., Wassenaarseweg 72, 2333 AL Leiden, The Netherlands
Mutat Res; 84(1):125-132 1981

The role of 5-bromodeoxyuridine (BrdUrd) incorporated into DNA on sister-chromatid exchanges (SCE) induced by inhibitors of poly-(ADP-ribose)-polymerase (PARP) was studied in Chinese hamster ovary (CHO) cells. Cells were grown in medium containing 5 uM BrdUrd to produce sister chromatids containing bifiliarly (BB) or unifiliarly (TB) substituted DNA. Other cultures were exposed to BrdUrd followed by thymidine (TdR) to produce unifiliarly substituted (TB) or unsubstituted (TT) DNA. Exposure to 3-aminobenzamide (3-AB: 0-10 uM) induced SCE in a dose-dependent manner (6.45-54.10 SCE/cell). Benzamide (BA) also produced dose-dependent SCE. Frequencies of SCE were doubled when 3-AB was present during the first cell cycle; the increase was six-fold when 3-AB was present during the second cell cycle. The increase was additive when 3-AB was present during both cycles. The DNA template used for replication, but not the presence of TdR or BrdUrd in the medium, was critical for induction of SCE. Both 3-AB and BA inhibited PARP. Results after reversal of DNA labeling patterns indicated that the presence of BrdUrd, rather than cell cycle number, was directly related to SCE. Mutations to HGPRT- were not increased by 3-AB or BA. Since 3-AB and BA produced SCE, but not point mutations, the SCE test may produce false positive results in mutagenicity tests. (13 Refs)

13. EFFECT OF 1,2-DIMETHYLHYDRAZINE AND DIETHYLNITROSAMINE ON CELL REPLICATION AND UNSCHEDULED DNA SYNTHESIS IN TARGET AND NONTARGET CELL POPULATIONS IN RAT LIVER FOLLOWING CHRONIC ADMINISTRATION.

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Cancer Res; 42(1):89-92 1982

Marked differences in the rates of de novo DNA synthesis and unscheduled DNA syn thesis were observed in hepatocytes and nonparenchymal cells (NPC) isolated from Fischer 344 rats following in vivo exposure to 1,2-dimethylhydrazine (SDMH) or diethylnitrosamine (DEN) for 1.5, 4, 8, 16, and 28 days. Liver cells were labeled in vivo with bromodeoxyuridine and [3H]thymidine, following which, hepatocytes and NPC were separated by elutriation centrifugation. Purified DNA was then separated into fully replicated and nonreplicated DNA by ultracentrifugation in CsCl gradients. Following exposure to SDMH, the rate of de novo DNA replication in NPC was greatly inc reased over both control NPC and the corresponding hepatocytes for the entire time course. Unscheduled DNA synthesis was only observed in hepatocytes after exposure to SDMH. Following exposure to DEN, both cell populations exhibited changes in de novo DNA synthesis that were directly proportional to one another except at 1.5 days. Increases occurred first in hepatocytes at 1.5 days but were delayed in NPC until 4 days. Hepatocyte replication returned to control values by 28 days. Unscheduled DNA synthesis was much lower following exposure to DEN than SDMH. There-

fore, SDMH, which induces hemangioendotheliomas of the liver at the dose given, induces a marked increase in cell replication in the target cell population and unscheduled DNA synthesis in the resistant cell population. DEN, which induces hepatocellular carcinoma, moderately stimulates cell replication in both liver cell populations and induces little unscheduled DNA synthesis in either population. (Author abstract) (19 Refs)

14. TISSUE-DEPENDENT ENZYME-MEDIATED REPAIR OR REMOVAL OF O-ETHYL PYRIMIDINES AND ETHYL PURINES IN CARCINOGEN-TREATED RATS.

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Carcinogenesis; 2(10):1069-1073 1981

Ten-day-old BD IX rats were injected with radiolabeled N-ethyl-N-nitrosourea (EtNU: 69.4 ug/kg, ip), and the sites and proportions of ethyl products, as well as their removal and repair, in DNA from various tissues was examined. One hr after carcinogen injection, DNA of brain, liver, and other pooled organs (spleen, lung, thymus, muscle, and intestine) showed similar proportions of the derivatives quantitated (O6-ethyl [Et] guanine [G], 7EtG, 3-Et adenine [A], O2-Et thymine [T], O4-EtT, O2-Et cytosine [C], and ethylphosphotriesters). During the 75 hr after carcinogen administration, most ethylated bases were poorly removed (or, in the case of O4-EtT, not at all) from DNA in the brain (the target tissue of EtNU carcinogenicity), and from DNA in the tissue pool. Removal from the brain appeared to cease after 25-50 hr. Kinetics of O6-EtG removal in brain and in the tissue pool were similar, except that there was a rapidly exhausted early and partial repair capability in brain. O-alkyl products were re moved from the liver at progressively increasing rates over the entire 75-hr period. The accelerated loss of O2-EtT, O4-EtT, and O2-EtC may have been due either to an increase in hepatic protein synthesis as a result of recovery from EtNU-induced inhibition or to induction of an O-alkyl pyrimidine-specific enzyme. Triester levels remained almost unchanged in all tissues examined. However, the small decrease in the triester level observed in liver DNA suggested a half-life of greater than 1 wk. Any or all persistent promutagenic derivatives (O6-EtG, O2-EtT, O4-EtT, O2-EtC) may be important in initiation of carcinogenesis by somatic mutation. (45 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN INVERTEBRATES AND LOWER EUKARYOTES

15. EVIDENCE FOR DNA DOUBLE-STRAND BREAKS AS THE CRITICAL LESIONS IN YEAST CELLS IRRADIATED WITH SPARSELY OR DENSELY IONIZING RADIATION UNDER OXIC OR ANOXIC CONDITIONS.

Frankenberg D, Frankenberg-Schwager M, Blocher D, Harbich R
Gesellschaft fur Strahlen-und Umweltforschung mbH, Institut fur Biologie, Abteilung fur Biophysikalische Strahlenforschung, Paul-Ehrlich-Strasse 20, D-6000 Frankfurt/Main, W. Germany
Radiat Res; 88(3):524-532 1981

The number of DNA double-strand breaks (dsb)/lethal event was determined under oxic and anoxic conditions and at different ionizing densities in a yeast mutants homozygous for the rad 52 gene. This mutant is not capable of repairing dsb and displays a high sensitivity ionizing radiation. The results indicated that not only the type but also the number of lesions required to kill a rad 52 cell may be identical irrespective of the ionization density of radiation used and oxic or anoxic conditions. (17 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN BACTERIA

16. STUDIES ON CHEMICAL CARCINOGENS. XX. INHIBITORY EFFECT OF ALKYL ISOCYANATES AND ISOTHIOCYANATES IN E. COLI BY ULTRAVIOLET RADIATION.

Kawazoe Y, Kato M, Takahashi K
Faculty Pharmaceutical Science, Nagoya City Univ., 3-1 Tanabedori, Mizuho-ku, Nagoya 467, Japan
Chem Pharm Bull (Tokyo); 29(9):2631-2638 1981

It was observed that treatment of H/r30R cells with alkyl isocyanates or isothiocyanates altered the mutability of such cells exposed to uv irradiation. Hs30R cells were not affected by treatment with these compounds. It is suggested that these compounds extended the period of time during which excision repair could be carried out. (18 Refs)

MACROMOLECULAR BINDING OF CARCINOGENS

17. THE DISTRIBUTION OF BENZO(A)PYRENE DNA ADDUCTS IN MAMMALIAN CHROMATIN.

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Chemical Carcinogenesis Div., Inst. Cancer Res., Pollards Wood Res. Station, Nightingales Lane, Chalfont St. Giles, Bucks HP8 4SP, England
Nucleic Acids Res; 9(21):5533-5552 1981

This paper describes the distribution of DNA-lesions generated by the potent car cinogen benzo(a)pyrene (BP) or its ultimate metabolic derivative 7alpha,8beta,di-hydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene (BPDE) within mammalian chromatin using the enzymic probe micrococcal nuclease. We have shown that the progress of the nuclease on naked DNA is unaffected by the presence of the hydrocarbon lesion at moderate extents of digestion. Digestion of nuclei isolated from murine erythroleukemic cells immediately following BPDE treatment, and analysis of micrococcal nuclease resistant DNA by TCA precipitation, hydroxyapatite chromatography and gel electrophoresis demonstrates a non-random distribution of lesions. Approx 3x more binding occurs on the linker DNA regions between nucleosome cores than on the nucleosome core DNA itself. A similar result was obtained with BPDE treated primary mouse embryo cells; however nuclei isolated from these cells after prolonged treatment with BP (to allow metabolic activation) showed no such preferential binding. Post-treatment incubation of PBDE-treated cells shows that this difference can be accounted for by the loss of preferential localization with time. (Author abstract) (33 Refs)

18. THE ACTIVATION OF AFLATOXIN B1 IN LIVER SLICES AND IN BACTERIAL MUTAGENICITY ASSAYS USING LIVERS FROM DIFFERENT SPECIES INCLUDING MAN.

Booth SC, Bosenberg H, Garner RC, Hertzog PJ, Norpoth K
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Carcinogenesis; 2(10):1063-1068 1981

Activation of aflatoxin B1 (AFB1) was compared in two in vitro systems: binding to DNA in liver slices incubated with 14C- or 3H-AFB1 and in standard bacterial mutation systems using 9000 x gravity supernatant (S-9) fractions from uninduced livers for activation. The results were compared in several rodent species in an effort to correlate them with known trends in carcinogenicity. Covalent binding of 14C-AFB1 to DNA from liver slices showed the order rat greater than hamster greater than mouse. Phenobarbitone pretreatment of rats decreased binding, and binding of aflatoxin G1 (AFG1) was less than that of AFB1. These findings all were correlated with relative susceptibility to AFB1-induced hepatocarcinogenesis. An exception to this trend was the similar level of binding found in male and female rat livers. Levels of 3H-AFB1 binding to DNA in human liver biopsies ranged from 0.7-8.5 nanog AFB1/mg DNA, which was similar to the range seen in the mouse and hamster. Mutagenicity data did not correlate with carcinogenicity in relation to species differences, as the efficiencies of livers from the three species for activating AFB1 mutagenicity were hamster greater than rat greater than mouse. AFG1 mutagenicity generally was markedly less than that of AFB1 when activated by rat liver S-9. The correlation between AFB1 binding to DNA in liver slices in various rodent species and susceptibility to AFB1 hepatocarcinogenesis and its modification in the rat by phenobarbitone suggests that these differences are related to differences in metabolic activation of AFB1 to its reactive species, its subsequent detoxification, and macromolecular interaction. (30 Refs)

19. PHOTOINDUCED REACTION OF DIMETHYLNITROSAMINE WITH DNA AND POLYNUCLEOTIDES.

Arfellini G, Prodi G, Rocchi P, Grilli S
Centro di Cancerogenesi Chimica, Istituto di Canerologia, Universita degli Studi di Bologna, via S. Giacomo 14, 40126 Bologna, Italy
Photochem Photobiol; 34(5):645-648 1981

Products from dimethylnitrosamine (DMN) photolysis were found to bind with DNA and with synthetic polynucleotides, and some of the interaction compounds were identified. When DNA or polynucleotides were incubated with 14C-DMN and simultaneously subjected to UV irradiation at 334 nanometer covalent binding to DNA increased with time. Binding with polyguanylic acid poly(G) was 36-fold higher than that with other polynucleotides. These interactions occurred only if nucleic acids were present during DMN photolysis. Trimethylamine was the interaction product recovered in alkaline hydrolysates of polyadenylic acid, polyuridylic acid, polycytidylic acid and poly and poly(A) following the photoinduced reaction with labeled DMN. Both trimethylamine and N-methylhydrazine were recovered after the reaction of DMN with DNA and with poly(G). This physicochemical system could serve as a model of chemical carcinogenesis. (31 Refs)

20. IN VITRO REACTION OF THE CARCINOGENIC DERIVATIVE N-ACETOXY-7-ETHYL-N-2-ACETYLAMINOFLUORENE WITH DNA. A SPECTROSCOPIC STUDY.

Saint-Ruf G, Spodheim-Maurizot M, Loukakou PE, Coic JP
Centre de Biophysique Moleculaire, CNRS, 1A, avenue de la Recherche Scientifique, F-45045 Orleans cedex, France
Carcinogenesis; 2(10):1019-1025 1981

Reaction in vitro of DNA with N-acetoxy-7-ethyl-N-acetylaminofluorene (N-AcO-EtAAF) was compared with N-acetoxy-N-acetyl-2-aminofluorene (NAcO-AAF). Introduction of an ethyl group at position 7 of the fluorene ring induces an increase of reaction of this (model) metabolite of the carcinogen 2-acetoxy-2-aminofluorene (2-AAF) toward DNA and its constituents. UV absorption and circular dichroism spectroscopic methods were used to characterize the DNA reacted with N-AcO-EtAAF (DNA-EtAAF). Results indicate some conformational similarities between native DNA-EtAAF and DNA-AAF such as the presence of destabilized regions around the bound carcinogen and of stacking interactions between these residues and the adjacent nucleotides. Important differences appear to exist between adducts or modified sequences in native as compared to denatured DNA (contrary to DNA-AAF and DNA bearing covalently bound 2-aminofluorene). (19 Refs)

21. HOT SPOTS OF FRAMESHIFT MUTATIONS INDUCED BY THE ULTIMATE CARCINOGEN N-ACETOXY-N -2-ACETYLAMINOFLUORENE.

Fuchs RP, Schwartz N, Daune MP
Laboratoire de Biophysique, Institut de Biologie Moleculaire et Cellulaire du CNRS, 15 rue Rene Descartes, 67084 Strasbourg Cedex, France
Nature; 294(5842):657-659 1981

An important step in carcinogenesis is thought to be the initial attack of the DNA molecule by a so-called ultimate carcinogen. More than 90% of the carcinogens tested have been found to be mutagens in bacterial systems. The covalent binding of the ultimate carcinogen to the DNA bases or phosphate groups creates a premutational lesion that in vivo is processed by the repair, replication and recombination enzymes, and eventually may be converted into a mutation. Being interested in the way that an initial premutational event is converted into a stable heritable mutation, we have sequenced stable mutations in a gene that has formed covalent adducts in vitro with N-acetoxy-N-2-acetylaminofluorene (N-AcO-AAF, a model for the ultimate metabolite of the rat liver carcinogen 2-acetylaminofluorene AAF). We show here that the mutations are mainly frameshifts involving G-C base pairs, and that certain base pairs (hotspots) are affected at relatively high frequencies. These results fit a model in which N-AcO-AAF-modified guanine acts as a non-coding base that during replication results in deletion of the modified residue. (Author abstract) (23 Refs)

22. FORMATION OF MACROMOLECULAR COMPLEXES AND OTHER EFFECTS OF DNA TREATMENT WITH DIETHYL AND DIMETHYL SULFATE: PHYSICOCHEMICAL AND ELECTRON MICROSCOPIC STUDIES.

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Carcinogenesis; 2(10):981-990 1981

Production of macromolecular complexes by DNA exposed to diethylsulfate (diES) or dimethylsulfate (diMS) was investigated by a variety of techniques. A fraction of DNA treated briefly with diES or diMS moves during velocity centrifugation experiments less rapidly than most of the control, untreated DNA and more rapidly through gels during electrophoresis. This apparent decrease in size is paralleled by formation of large DNA aggregates with mobilities indicating mol wt several times that of control DNA. Basic protein in the mixture increases the rate of formation of such complexes. Alkylated DNA tends to bind to both biological and non-biological materials, as indicated by increased attachment of DNA to columns built with methyl-esterified serum albumin and in its quantitative retention on nitrocellulose filters. DNA exposed to diMS decreases its density in CsCl gradients. A mixture of two or more DNAs of different densities exposed to diMS produces a UV-absorbing band which is found in such gradients at an intermediate density. When the alkylation reaction is carried out in the presence of a protein, a portion of DNA bands at a density intermediate between that of the DNA and the protein, even in the presence of an ionic detergent. Electron microscopy of the alkylated DNA shows multiple single-strand breaks and peel-off whiskers of denatured DNA. Aggregates of DNA molecules become visible upon further incubation of DNA with the alkylating agent. It is suggested that the DNA-DNA and DNA-protein complexes play an important role in carcinogenesis and mutagenesis. (22 Refs)

23. ALKYLATION OF N2 IN DEOXYGUANOSINE BY DEHYDRORETRONECINE, A CARCINOGENIC METABOLITE OF THE PYRROLIZIDINE ALKALOID MONOCROTALINE.

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Cancer Res; 42(1):8-14 1982

Dehydroretronecine, an antimitotic and carcinogenic agent, reacted with the deoxyguanosine at pH 7.4 in vitro to yield in nearly equal quantities two major adducts, which were isolated by thin-layer and high-pressure liquid chromatography. The adducts were stable at pH 8.7 and 30 C for at least 24 hr, showed pKas at acidic and alkaline pHs, reacted with 4-(p-nitrobenzyl)-pyridine, had a nonexchangeable guan-8-yl proton, and contained equimolar quantities of the pyrrole and nucleotide moieties. From the above data and comparison of proton magnetic resonance spectra of dehydroretronecine, deoxyguanosine, and the adducts, both products were identified as derivatives with a bond between C-7 of dehydrosupinidine and N2 of deoxyguanosine. Mass spectral fragmentation patterns and infrared and UV absorbance spectra were also consistent with N2 substitution. Circular dichroism spectra established the identities of each of the adducts as 7-(deoxyguanosin-N2-yl)dehydrosupinidine; they are enantiomeric at C-7. These results demonstrate that the reactive electrophile derived from protonated dehydroretronecine readily alkylates the N2 position of deoxyguanosine at C-7 in an SN1 reaction to yield a racemic mixture of products. (Author abstract) (34 Refs)

24. SAFROLE: ITS METABOLISM CARCINOGENICITY AND INTERACTIONS WITH CYTOCHROME P-450.

Ioannides C, Delaforge M, Parke DV
Dept. Biochemistry, Univ. Surrey, Guildford, Surrey GU2 5XH, England
Food Cosmet Toxicol; 19(5):657-666 1981

This review of safrole metabolism is aimed at elucidating the importance of the allyl moiety and the methylenedioxy group in the mechanism of carcinogenesis. It includes studies concerning safrole carcinogenicity, interactions of safrole with cytochrome P-450, inhibition of mixed-function oxidase activity by safrole, ligand complex formation with cytochromes P-450 and P-448, and hemoprotein formation by safrole and isosafrole. Ligand complexing and covalent binding of reactive intermediates with the heme and protein moieties, respectively, of cytochrome P-450, may be fundamental to the mechanism of safrole carcinogenesis. Structural and functional properties of the cytochrome are substantially changed by this binding, which, since ribosomes are attached to the endoplasmic reticulum at cytochrome P-450, may be associated with loss of ribosomes known to occur following treatment with safrole or other carcinogens. Chemical carcinogenesis is associated with increases in hepatic cytochrome P-448 and simultaneous loss of cytochrome P-450 activity and could, through loss of ribosomes, result in impairment of glycoprotein synthesis and thus contribute to malignant transformation by epigenetic mechanism. Therefore, of the two functional groups of safrole, the allyl group has been shown to be associated with mutagenicity, and the methylenedioxy moiety to be associated with changes to cytochrome P-450 and possibly with epigenetic aspects of carcinogenicity. (84 Refs)

EFFECT OF CARCINOGENS ON MACROMOLECULAR SYNTHESES

25. SELECTIVE EFFECTS OF METAL IONS ON RNA SYNTHESIS RATES.

Niyogi SK, Feldman RP, Hoffman DJ
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Toxicology; 22(1):9-21 1981

Fourteen chloride metal ions were tested in vitro to determine their effects upon Escherichia coli RNA polymerse transcription of calf thymus and T4 phage DNA. Conditions were altered from previously published reports to insure that metal ions were kept in soln (pH 7.4, omissions of 2-mercaptoethanol). Neither overall synthesis nor chain initiation were altered by the new assay conditions. Increasing concentrations of metal ions inhibited transcription in the order Pb2+ greater than Zn2+ greater than Cu2+ greater than Cd2+ greater than Ni2+ greater than Ca2+ greater than Co2+ greater than Mn2+. Be2+ had a stronger inhibitory effect than Cd2+ at low concentrations but less so at higher concentrations. Sr2+ had very little effect. At concentrations of Ca2+, Mg2+, Sr2+, Zn2+, Li+, Na+, and K+, that decreased overall transcription chain initiation was also decreased. These metals are considered to be non-mutagenic and non-carcinogenic. CO2+, MN2+, and Cd2+, metals that are mutagenic and carcinogenic, caused marked stimulation in chain initiation at concentrations that inhibited overall transcription. BeC12 and PbC12, both known carcinogens, caused only a wide range of concentrations that inhibited overall transcription. (42 Refs)

26. A TRANSIENT POST-IRRADIATION DEFECT IN NEWLY SYNTHESISED DNA.

Cramp WA, George AM, Lunec J, Harris G, Olsen I, Lewis PD, Chamberlain S, Ahnstrom G, Erixon K
MRC Cyclotron Unit, Hammersmith Hosp., London W12 0HS, England
Int J Radiat Biol; 40(5):573-579 1981

Ionizing radiation induced a dose-dependent increase in single-stranded DNA level in radiation-resistant and -sensitive mouse lymphoma cells and in skin fibroblasts from normal donors and F riedreich's ataxia patients. Return to background level occurred without further strand breakage and was interpreted as a rearrangement of the perturbed DNA. (20 Refs)

27. EFFECT OF ACTIVATORS OF CAMP ACCUMULATION ON DIFFERENT STAGES OF GENOME EXPRESSION DURING ACUTE RADIATION INJURY. COMMUNICATION 2. EFFECT OF SEROTONIN AND PAPAVERINE ON TEMPLATE ACTIVITY OF NUCLEAR CHROMATIN FROM LIVERS AND SPLEENS OF RATS SUBJECTED TO WHOLE-BODY X-IRRADIATION.

Tsudzevich BA, Galkina LA, Kucherenko NE
Faculty Biology, T. G. Shevchenko State Univ., Kiev, USSR
Radiobiologiia; 21(5):654-659 1981

Administration of serotonin (ST) and papaverine (PV) to rats prior to whole-body x-irradiation prevented the inhibition of template activity of spleen chromatin and stimulated the template activity of liver chromatin. It was suggested that the radioprotective effect of activators of cyclic AMP is associated with increased radioresistance of early stages of genome expression. (11 Refs) (In RUS)

28. IDENTIFYING HUMAN CELLS CAPABLE OF METABOLIZING VARIOUS CLASSES OF CARCINOGENS.

Aust AE, Antczak MR, Maher VM, McCormick JJ
Dept. Microbiology, Michigan State Univ., East Lansing, MI, 48824
J Supramol Struct; 16(3):269-279 1981

Metabolism of tritiated benzo(a)pyrene (BP) to aqueous-acetone soluble forms and inhibition of cellular DNA synthesis were used to identify human cells capable of metabolizing various classes of carcinogens. Hydrocarbon-metabolizing activity assay (HMAA) and DNA synthesis inhibition assay were optimized and the results on 15 human epithelial cell lines were compared. Four classes of carcinogens were examined: polycyclic hydrocarbons (PH), aromatic amines (AA), heterocyclic hydrocarbons, and nitrosamines. Each of the classes was activated by one or more cell lines. Cells with very low metabolizing activity, such as NF, showed little or no cytotoxic response when exposed to BP at concentrations up to 30 uM for 48 hr. Biological results (cytotoxicity, mutagenicity, and DNA binding) suggest that the HMAA is a useful prescreen for identifying human cells that metabolize BP to biologically active forms. Cells that appeared capable of metabolizing PH or AA according to the methods were found to produce metabolites which were cytotoxic to cocultivated human xeroderma pigmentosum fibroblasts after 48 hr exposure to the carcinogen. (28 Refs)

29. EFFECTS OF INHIBITORS OF DNA SYNTHESIS AND PROTEIN SYNTHESIS ON THE RATE OF DNA SYNTHESIS AFTER EXPOSURE OF MAMMALIAN CELLS TO ULTRAVIOLET LIGHT.

Griffiths TD, Dahle DB, Meechan PJ, Carpenter JG
Dept. Biological Sciences, Northern Illinois Univ., De Kalb, IL, 60115
Biochim Biophys Acta; 656(1):55-61 1981

Chinese hamster V-79 cells were treated with metabolic inhibitors of DNA or protein synthesis for various intervals of time after exposure of 3.0 or 5.0 J.m-2. After removal of the metabolic block(s) the rate of DNA synthesis was followed by measuring the incorporation of [14C]thymidine into acid-insoluble material. A 2.5 or 5.0 hr incubation with cycloheximide or hydroxyurea was effective in delaying the onset of the recovery in the rate of DNA synthesis that normally becomes evident several hr after exposure to UV light. By using concentrations of cycloheximide or hydroxyurea that inhibit DNA synthesis by a similar amount (70%), but protein synthesis by vastly different amounts (95% for cycloheximide; 0% for hydroxyurea), it was apparent that the delay in recovery caused by the treatment of the cells with cycloheximide could be accounted for entirely by its inhibitory effect on DNA synthesis. This suggests that the recovery in DNA synthetic rates following exposure of V-79 cells to UV light does not appear to require de novo protein synthesis, and therefore does not appear to require the involvement of an inducible DNA repair process. (Author abstract) (27 Refs)

30. 4,4'-DIMETHYLANGELICIN, A MONOFUNCTIONAL FUROCOUMARIN SHOWING HIGH PHOTOSENSITIZING ACTIVITY.

Baccichetti F, Bordin F, Carlassare F, Peron M, Guiotto A, Rodighiero P, Dall'Acqua F, Tamaro M
Inst. Pharmaceutical Chemistry, Padua Univ., Padua. Italy
Photochem Photobiol; 34(5):649-651 1981

A new angelicin derivative, 4,4'-dimethylangelicin, showed high photosensitizing activity. The compound had a high lethal effect in Escherichia coli B48, was mutagenic in E coli WP2, was phototoxic on guinea pig skin, and inhibited DNA synthesis in Ehrlich ascites tumor cells. (15 Refs)

31. CATABOLISM OF DESIALYLATED GLYCOPROTEINS DURING CARCINOGENESIS AND INFLAMMATION IN RATS.

Osada J, Zawirska B, Chorazyczewski J, Dobryszycka W
Dept. Biochemistry, Inst. Bioanalysis and Environmental Res., Medical Sch., Szewska 38/39, 50-139 Wroclaw, Poland
Acta Biochim Pol; 28(2):147-156 1981

Binding of desialylated haptoglobin and orosomucoid was studied in rat liver undergoing carcinogenesis due to an implanted, aflatoxin B1-induced hepatoma, and inflammation due to injection of turpentine. Biochemical studies of binding of asialo-glycoproteins were performed 4 and 8 days after tumor cell implantation or turpentine injection. In studies of catabolism, asialo-[125I]haptoglobin and asialo[125I]orosomucoid were injected iv and blood radioactivity was measured over a period 1-15 min just prior to sacrifice. Determinations were made of seromucoid, haptoglobin, sialic acid, and fucose in blood serum; binding of sialo-glycoproteins by liver extracts; and elimination of labeled haptoglobin and orosomucoid from the circulation. Hepatoma and inflammation had no effect on the activity of liver receptors for asialo-glycoproteins, nor the

rate of asialo-glycoprotein elimination from the c irculation. (28 Refs)

REVIEWS

32. THE REPAIR OF DNA DAMAGE: RECENT DEVELOPMENTS AND NEW INSIGHTS.

Friedberg EC, Bonura T, Love JD, McMillan S, Radany EH, Schultz RA
Dept. Pathology, Lab. Experimental Oncology, Stanford Univ., Stanford, CA, 94305
J Supramol Struct Cell Biochem; 16(1):91-103 1981

Recent research into enzymatic repair of base damage to DNA is reviewed. Escherichia coli and its phages have been the most suitable model systems for this research. Seven distinct DNA glycosylases have been isolated from E coli. These glycosylases are specific for particular types of DNA damage and catalyze hydrolysis of the N-glycosylic bond between nitrogenous bases and the deoxyribose-phosphate backbone of the DNA molecule. Apurinic/aprymidine (AP) endonucleases effect incision of DNA sites from which damaged bases have been removed by the glycosylases. AP nucleases may vary in their substrate specificity and for the direction of operation (5' or 3' action). UV endonucleases (EN) have been isolated from E coli infected with M luteus and T4 phages. UV EN catalyze the removal of UV-induced pyrimidine dimers. UV EN of E coli consists of a complex of products from the uvrA, uvrB, and uvrC genes. At least the uvrA and uvrB proteins are inducible and normally exist in very small amounts. An inducible, apparently error-free DNA repair pathway has been reported in E coli that produces a reduction in mutation rates and increases survival after pre-exposure to very low levels of mutagenic alkylating agents. Preliminary evidence suggests that DNA repair systems found in E coli may have similar, possibly more complex counterparts in eukaryotic systems. (75 Refs)

33. GENETIC AND BIOCHEMICAL STUDIES WITH ATAXIA TELANGIECTASIA.

Huang PC, Sheridan RB
Dept. Biochemistry, Sch. Hygiene and Public Health, Johns Hopkins Univ., Baltimore, MD, 21205
Hum Genet; 59(1):1-9 1981

Correlation of the clinical symptomatology with the genetics and biochemical studies of cultured cells derived from patients with ataxia telangiectasia (AT) is presented in a review. The genetics and symptomatology of AT are described. The susceptibility of patients with AT to sino-pulmonary infection and predisposition toward lymphoreticular malignancy may be caused by immunodeficiency involving humoral and/or the cellular immune system. Approx 10% of patients with AT develop cancer. Response of AT patients to radiation is discussed. Recent cytogenetic, cellular, and biochemical studies are reviewed which support the hypothesis that a defect in DNA repair is responsible for the many manifestations of AT. A table summarizes biochemical studies of 25 factors in 19 cell lines, all but four of which were derived from AT homozygotes. The biochemical evidence indicates that the defect specifically reduces the cell ular capacity to remove bases and nucleotides damaged by ionizing radiation, without affecting the cells' ability to scavenge free radicals or to rejoin breaks in the sugar-phosphate backbone of DNA. (72 Refs)

34. GENETIC AND NONGENETIC EVENTS IN NEOPLASIA.

Stott WT, Reitz RH, Schumann AM, Watanabe PG
Toxicology Res. Lab., Dow Chemical USA, Midland, MI, 48640
Food Cosmet Toxicol; 19(5):567-576 1981

Mechanisms of chemically induced carcinogenesis, based on the degree of carcinogen interaction with DNA, are discussed in relation to risk assessment. Carcinogens interacting directly with DNA are classified as genotoxic, whereas those that do not directly interact with cellular DNA are classified as epigenetic. In either case, the mechanism may or may not involve a mutational event. Chemicals with strictly genetic activity are often those that either are, or can be activated to, strongly electrophilic species. Chemicals with intermediate activity may have both a genetic and an epigenetic component, and some chemicals, that show little or not genetic activity may produce tumors strictly through recurrent cytotoxicity or other epigenetic mechanisms. Recurrent cytotoxicity is an epigenetic mechanism which involves increased regenerative DNA synthesis in response to tissue injury and is believed to result in enhancement of the normal spontaneous mutation rate. Two parameters used in the authors' laboratory for identifying a genetic effect are DNA damage, measured by DNA alkylation in vivo, and DNA repair. For evidence of epigenetic, cytotoxic effects, DNA synthesis in the target tissue is measured and classic histopathologic examination is carried out. The results of the carcinogen bioassay on perchloroethylene, chloroform, and 1,4-dioxane are presente; these studies indicated that these agents may cause tumors in laboratory animals via an epigenetic-cytotoxic mechanism. Tumor induction in rats by repeated administration of high doses of 1,4-dioxane may involve more than one epigenetic mechanism. Consideration of data concerning the possible mechanism of carcinogenicity of a chemical, along with pharmacokinetic data, will allow better understanding of bioassay results and more accurate assessment of carcinogenic risk. (62 Refs)

35. STRUCTURE-MUTAGENICITY ANALYSIS WITH THE CHO/HGPRT SYSTEM.

Hsie AW
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Food Cosmet Toxicol; 19(5):617-621 1981

A mutational system which affects hypoxanthine-guanine phosphoribosyl transferase (HGPRT) activity in Chinese hamster ovary (CHO) cells, the CHO/HGPRT system, was used to study the structure-mutagenicity of 10 carcinogenic alkylating agents and 6 platinum(11) compounds. Cytotoxic and mutagenic effects of the alkylating agents decreased with increasing size of the alkylating group. When t he relationship between DNA alkylation and mutation at the hgprt locus of N-nitroso-N-methylurea (MNU) and N-nitroso-N-ethylurea (ENU) was studied, MNU, on an equimolar basis, had 15x the alkylating activity of ENU but only 3x the mutagenic activity. Ethylation of DNA by ENU resulted in greater than 4x the number of mutagenic lesions than did methylation by MNU. cis-Dichlorodiammine platinum(11) was the most mutagenic among the six platinum(1)chloroammines, while its steric isomer, the trans form, was non-mutagenic. Mutagenicity and cytotoxicity differ in their reactivity of DNA binding. The mutation induction by the cis isomer as a function of treatment concentration was 2400x that of the trans isomer. However, the cis isomer bound only 3x more to cellular DNA than did the trans isomer. The mutant yield per molecule bound to DNA was 800x larger for the cis than for the trans isomer. Cytotoxicity per DNA lesion was a factor of 9 greater for the cis than for the trans isomer.

These studies demonstrate that both the quantity and quality of DNA adducts affect mutagenicity and cytotoxicity. The CHO/HGPRT system is useful for studying genetic aspects of toxicology and for relating molecular parameters necessary for mutagenic and cytotoxic activities. (26 Refs)

36. ON THE MOLECULAR BASIS OF ONCOGENESIS.

Ahlgren JD
Div. Medical Oncology, Vincent T. Lombardi Cancer Res. Center, Georgetown Univ. Sch. Medicine, Washington, DC, 20007
J Theor Biol; 93(1):215-223 1981

A molecular basis for the development of neoplasia is proposed based on viral disruption of genomic regions coding for proteins which control entry into the cell cycle from Go. Such disruption could also be effected by chemically or radiation-induced mutation. Under such conditions normal control proteins would no longer be synthesized. As the available intracellular pool of normal protein is used up, more and more cells would remain in the proliferative cycle. Fetal genes might also be derepressed, with a concomitant reduction in the expression of adult genes, resulting in a shift in transformed cells toward a less differentiated state. The expression of derepressed fetal genes would account for observed fetal antigens on tumor cells. The somatic cell destined to form a tumor clone may have multiple abnormal intracellular proteins due to the random nature of simultaneous point mutations in the genome. Endogenous transposable elements may also cleave control cistrons. (35 Refs)

37. CHEMICAL CARCINOGENESIS.

Farber E
Dept. Pathology, Univ. Toronto, 100 College St., Toronto, ON M5G 1L5, Canada
N Engl J Med; 305(23):1379-1389 1981

Fundamental concepts related to the causation, prevention, and therapy of cancer in humans are reviewed, with emphasis on mechanistic aspects. Topics include cancer as a chronic multistage p rocess, initiators and initiation (initiators, activation and metabolism of procarcinogens, possible molecular targets for ultimate carcinogens, DNA repair, carcinogen metabolism in human tissues, initiation), promoters and promotion (promoters, promotion, subsequent steps - progression and transfection, diet and carcinogenesis, chemotherapy and carcinogenesis), and new bioassays for carcinogens and promoters. Illustrations of (1) the current view on activation of benzo(a)pyrene to benzo(a)pyrene-7,8-dihydrodiol-9,10-epoxide, (2) sites of interactions of activated forms of carcinogens with the four DNA bases, and (3) steps in the initiation of carcinogenesis with chemicals are presented. Later phases of chemical carcinogenesis, ie post-initiation phenomena including promotion, and the relative quantitative importance of exogenous or endogenous chemical carcinogens in patients with cancer not related to smoking are not sufficiently understood. (118 Refs)

38. THE DECISION-POINT APPROACH FOR SYSTEMATIC CARCINOGEN TESTING.

Weisburger JH, Williams GM
Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Food Cosmet Toxicol; 19(5):561-566 1981

The decision-point approach provides a framework, based on current concepts of the mechanisms of carcinogenesis, for systematic evaluation of potential mutagenic and carcinogenic hazards of chemicals. Chemical carcinogens have been divided into two main categories-genotoxic agents, which interact with DNA and genetic material and lead to irreversible alterations in DNA, and epigenetic agents, which operate by distinct nongenotoxic mechanisms and are tissue-specific. Genotoxic agents include direct-acting carcinogens, procarcinogens, and inorganic carcinogens; the first two classes damage DNA either through direct chemical reactivity or following metabolism by enzyme systems, whereas inorganic carcinogens are not directly genotoxic but lead to changes in DNA by selective alteration in the fidelity of DNA replication. Epigenetic agents include solid-stage carcinogens, hormones, immunosuppressors, co-carcinogens, and promoters. The decision-point approach involves five steps: (1) consideration of the structure of the chemical; (2) in vitro short-term tests (mutagenesis, DNA repair, chromosome effects, and cell transformation); (3) limited in vivo bioassays (skin-tumor induction in mice, pulmonary-tumor induction in mice, breast-cancer induction in rats, induction of rodent liver altered foci, and assays for promoters); (4) chronic bioassay; and (5) final classification of a chemical as a genotoxic or epigenetic carcinogen. Health-risk analysis also must consider quantitative potential as well as qualitative positive or negative results. The proposed testing approach provides for systematic yet economical testing, the results of which can be applied to flexible, rational health-risk analysis. (26 Refs)

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Dept. Pathology, Univ. Toronto, 100 College St., Toronto, ON M5G 1L5, Canada
N Engl J Med; 305(23):1379-1389 1981

2. N-HEXANE AND ITS TOXICOLOGIC EFFECTS. A REVIEW.
Jorgensen NK, Cohr KH
Harevaenget 44, DK-4200 Slagelse, Denmark
Scand J Work Environ Health; 7(3):157-168 1981

3. SAFROLE: ITS METABOLISM CARCINOGENICITY AND INTERACTIONS WITH CYTOCHROME P-450.
Ioannides C, Delaforge M, Parke DV
Dept. Biochemistry, Univ. Surrey, Guildford, Surrey GU2 5XH, England
Food Cosmet Toxicol; 19(5):657-666 1981

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Dept. Radiation Medicine, Massachusetts General Hosp., Boston, MA, 02114
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6. NUTRITION AND CANCER: A REVIEW.
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Institut fur Sozial- und Praventivmedizin, Universitat Zurich, Gloriastrasse 32 B, 8006 Zurich, Switzerland
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Horowitz RM
U. S. Dept. Agriculture, Agricultural Res. Service, Fruit and Vegetable Chemistry Lab., Pasadena, CA, 91106
ACS Symp Ser; 170:43-59 1981

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8. ETIOLOGICAL CONCEPTS IN CERVICAL CARCINOGENESIS.
Kessler II
Dept. Epidemiology and Preventive Medicine, Univ. Maryland Sch. Medicine, 655 West Baltimore St., Baltimore, MD, 21201
Gynecol Oncol; 12(2,part2):S7-S24 1981

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Torres A, Martinez Guibelalde F, Gomez Garcia P, Garcia Castellano JM, Manzanares Escribano MR
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Sangre (Barc); 26(5B):700-717 1981
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10. CANCER FAMILY SYNDROME.
Svendsen LB, Bulow S
Kirurgisk-gastroenterologisk afdeling, Bispebjerg hospital, Copenhagen, Denmark
Ugeskr Laeger; 143(42):2713-2716 1981
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11. GENETIC AND BIOCHEMICAL STUDIES WITH ATAXIA TELANGIECTASIA.
Huang PC, Sheridan RB
Dept. Biochemistry, Sch. Hygiene and Public Health, Johns Hopkins Univ., Baltimore, MD, 21205
Hum Genet; 59(1):1-9 1981

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12. THE HEALTH EFFECTS AND ECOLOGICAL SIGNIFICANCE OF CHLORINE RESIDUALS IN WATER.
Kalmaz EV, Kalmaz GD
Univ. Tennessee, Univ. Station 8163, Knoxville, TN, 37916
Chemosphere; 10(10):1163-1175 1981

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Clin Gastroenterol; 10(3):755-771 1981

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Friedberg EC, Bonura T, Love JD, McMillan S, Radany EH, Schultz RA
Dept. Pathology, Lab. Experimental Oncology, Stanford Univ., Stanford, CA, 94305
J Supramol Struct Cell Biochem; 16(1):91-103 1981

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15. ROLE OF HORMONES INCLUDING DIETHYLSTILBESTROL (DES) IN THE PATHOGENESIS OF CERVICAL AND VAGINAL INTRAEPITHELIAL NEOPLASIA.
Robboy SJ, Truslow GY, Anton J, Richart RM
Dept. Pathology, Massachusetts General Hosp., Boston, MA, 02114
Gynecol Oncol; 12(2,part2):S98-S110 1981

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Honn KV, Bockman RS, Marnett LJ
Dept. Biological Sciences, Wayne State Univ., Detroit, MI, 48202
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Univ.-Hautklinik Eppendorf, Martinistr. 52, D-2000 Hamburg 20, W. Germany
Hautarzt; 32(11):601-606 1981
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BIOLOGICAL ASPECTS OF DNA ALTERATION AND REPAIR IN RELATION TO CARCINOGENICITY

1. DNA-REPAIR SYNTHESIS IN ATAXIA TELANGIECTASIA LYMPHOBLASTOID CELLS.

Ford MD, Houldsworth J, Lavin MF
Dept. Biochemistry, Univ. Queensland, Brisbane, 4067, Australia
Mutat Res; 84(2):419-427 1981

DNA-repair synthesis was assayed in lymphoblastoid cells from ataxia telangiectasia (AT) patients and from control cells following exposure to gamma-radiation (10-40 kilorad). NaI

HE 20.3173/2:

isopycnic gradient analysis and 3H-thymidine incorporation into acid-precipitable DNA in the presence of hydroxy urea indicated that AT heterozygote, AT homozygote, and control cells had similar capacities for repair of radiation damage. Rate and extent of dose-dependent inhibition of DNA replication by gamma-radiation were similar in the three groups of cells. Lack of difference between control and AT cells in degree of DNA-synthesis inhibition at the radiation doses used is likely due to a pronounced effect on overall DNA synthesis. (34 Refs)

2. AN APPARENT CORRELATION BETWEEN THE INHIBITION OF INDUCED ORNITHINE DECARBOXYLASE ACTIVITY BY GAMMA RADIATION AND THE CAPACITY FOR DNA REPAIR SYNTHESIS IN NORMAL AND ATAXIA TELANGIECTASIA HUMAN FIBROBLASTS: NO CORRELATION WITH CELL SURVIVAL.

Ben-Hur E, Kol R, Heimer YM, Shiloh Y, Tabor E, Becker Y
Dept. Radiobiology, Nuclear Res. Centre-Negev, P.O. Box 9001, Beer-Sheva, Israel
Radiat Environ Biophys; 20(1):21-28 1981

The effects of gamma radiation on induced ornithine decarboxylase (ODC) activity, DNA repair synthesis (DRS), and cell survival were studied in vitro in fibroblasts from normal individuals and patients with ataxia telangiectasia (AT). ODC activity in nonirradiated human fibroblasts was induced after a lag period of 2-3 hr by addition of fresh medium and reached a peak at 7-8 hr. A dose of 108 kilorad (krad) gamma radiation before induction substantially reduced ODC activity in normal cells of strain F107 and AT cells of strains F182 and F184. Cells of strain F196, from an apparently normal individual, showed much greater sensitivity than the other strains. F107 and AT cells showed an inhibition of DRS paralleling the decrease in induction of ODC. F196 cells showed a greater reduction in DRS capacity paralleling their greater inhibition of ODC induction. F107 and F196 showed similar cell survival curves after gamma irradiation (D37 values being 150 +-7 and 135 +-6 rad, respectively). AT cells were more sensitive than normal cells (D37 being 60 +-2 rad for F182 and 45 +-2 rad for 184). Apparently sensitivity of ODC induction and DRS are related, possibly in a causal manner, in normal and AT human fibroblast; cell survival is apparently not related to either ODC induction or DRS. (19 Refs)

3. INVESTIGATION OF THE SISTER CHROMATID EXCHANGE (SCE) FREQUENCY IN ONE PATIENT WITH XERODERMA PIGMENTOSUM.

Went M, Szorenyi A, Polay A, Simon N
(c/o Simon) Dept. Dermatology, Koranyi Fasor 8-10, H-6701 Szeged, Hungary
Arch Dermatol Res; 271(4):407-409 1981

The sensitivity of xeroderma pigmentosum (XP) cells from one patient to chemical mutagens was studied as a potential cytogenetic test. When the phytohemagglutinin-stimulated XP lymphocytes were exposed to mitomycin C prior to their first division, an increased rate of sister chromatid exchange (SCE) was observed. The high rate of SCE is a measurement of the amount of non-excisible or non-excised damage and consequently shows the altered capability of cells to repair DNA damage by a variety of physical and chemical factors. (14 Refs)

BIOLOGICAL ASPECTS OF DNA ALTERATION AND REPAIR IN RELATION TO MUTAGENICITY

4. MUTATION INDUCTION BY MONOCHROMATIC 254-NM AND 365-NM RADIATION IN STRAINS OF ESCHERICHIA COLI THAT DIFFER IN REPAIR CAPABILITY.

Webb RB, Turner MA
Div. Biological and Medical Res., Argonne Natl. Lab., 9700 South Cass Ave., Argonne, IL, 60439
Mutat Res; 84(2):227-237 1981

Tryptophan-independent revertants were induced by exposure to 254-and 365-nanometer monochromatic radiation in Escherichia coli strains WP2 (wild-type), WP2s (uvrA), WP6 (polA), and WP6s (polA uvrA) but not in WP5 (lexA), WP10 (reaA), or WP100 (recA uvrA). Data indicate that near-UV radiation produces mutations through the error-prone component of postreplicaton repair. Selective damage or inhibition to error-free and error-prone repair systems caused complete mutation responses at 365 nanometer. (35 Refs)

5. ULTRAVIOLET-INDUCED FRAMESHIFT MUTAGENESIS IN SALMONELLA TYPHIMURIUM: ABSENCE OF AN EFFECT OF MUTATION FREQUENCY DECLINE.

Leyden MF, Schoeffel KL, MacPhee DG
(c/o MacPhee) Dept. Microbiology, La Trobe Univ., Bundoora, Victoria 3083, Australia
Mutat Res; 84(2):247-255 1981

Yields of UV-induced back mutants to prototrophy were increased by nutrient broth in irradiated cells of Salmonella typhimurium frameshift strain LT2 hisC3076 (R46) and of an excision-deficient derivative of hisC3076 (R46) carrying the uvr-302 mutation, indicating that the broth effect does not depend upon excision repair. Classical mutation frequency decline had no significant influence on UV-induced frameshift mutagenesis under conditions identical to those in which it had a pronounced effect on UV-induced base-pair substitution mutagenesis. (19 Refs)

6. TESTS FOR MUTAGENICITY IN SALMONELLA AND COVALENT BINDING TO DNA AND PROTEIN IN THE RAT OF THE RIOT CONTROL AGENT O-CHLOROBENZYLIDENE MALONONITRILE (CS).

von Daniken A, Friederich U, Lutz WK, Schlatter C
Inst. Toxicology, Swiss Federal Inst. Technology, CH-8603 Schwerzenbach, Switzerland
Arch Toxicol; 49(1):15-27 1981

The aim of this study was to determine whether o-chlorobenzylidene malononitrile (CS) exhibits any genotoxic activity towards Salmonella or mammalian DNA in vivo. CS was synthesized with a [14C]-label at the benzylic carbon atom. It was administered ip at a dose level of 13 mg/kg (1 mCi/kg) to young adult male rats. Liver and kidney DNA was isolated after 8, 25, and 75 hr. The radioactivity was at (liver, 8 and 75 hr) or below (all other samples) the limit of detection of 3 dpm. Therefore, a possible binding of CS to DNA is at least 10(5) times lower than that of the strong hepatocarcinogen aflatoxin B1, and 4,0 00x lower than that of vinyl chloride. In contrast to this lack of DNA binding, but in agreement with the chemical reactivity of CS, a binding to nuclear proteins

could be detected with specific activities ranging between 50 and 121 dpm/mg for liver and between 3 and 41 dpm/mg for kidney. Protein binding could well be responsible for its pronounced cytotoxic effects. CS was also tested in the Ames Salmonella/microsome assay. Strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100 were used with or without pre-incubation. Only with strain TA 100 and only without pre-incubation, a doubling of the number of revertants was detectable at the highest dose levels used, 1,000 and 2,000 ug CS per plate. With pre-incubation of TA 100 with CS, a slight increase of the number of revertants was seen at 100 and 500 ug per plate, and a subsequent fall below control values at 1,000 ug. A check for the number of surviving bacteria revealed a strong bacteriotoxicity of the higher doses of CS so that the calculated mutation frequencies, ie, the number of revertants per number of surviving bacteria, increased with doses up to 500 ug. This toxicity could be counteracted in part by the addition of increasing amounts of rat liver microsomes. In the view of these results, and taking into account the rare and low exposure of man, it is concluded that CS will not create a risk for the induction of point mutations or of carcinogenic processes mediated by DNA binding. (Author abstract) (26 Refs)

7. LACK OF COMUTAGENICITY BY NORHARMAN AND OTHER COMPOUNDS ON REVERTANTS INDUCED BY PHOTOLABELING WITH 2-AZIDO-9-FLUORENONE OXIME.

White WE, Rock SG
Div. Molecular Biology, Univ. Alabama, Birmingham, AL, 35294
Mutat Res; 84(2):263-271 1981

Effects of several comutagenic or cocarcinogenic compounds on photolabel-induced mutagenesis were examined. Photolabeling with 2-azido-9-fluorenone oxime was used to produce mutagenic adducts directly, thereby bypassing metabolic requirements for aromatic amines. DNA-binding compounds ethidium, harman, and norharman at concentrations as low as 10(-6) M slightly reduced photolabel-induced mutagenesis in Salmonella typhimurium strain TA1538. Retinol (10(-6) to 10(-4) M) had no effect on mutagenesis or on toxicity. Cholic acid had no effect at concentrations less than 10(-5) M but decreased mutagenicity at 10(-4) M. Decreases in mutation rates could be a result of competition for binding sites, resulting in formation of fewer critical adducts. If this is true, binding of particular agents to DNA could be antimutagenic for some mutagens and comutagenic for mutagens with adducts at different positions. (22 Refs)

8. DIFFERENTIAL SUSCEPTIBILITY OF CANCER AND NORMAL DNA TEMPLATES ALLOWS THE DETECTION OF CARCINOGENS AND ANTI-CANCER DRUGS (ONCOTEST) (MEETING ABSTRACT).

Beljanski M, Le Goff L, Beljanski MS
Laboratoire de Pharmacodynamie, 92290 Chatenay-Malabry, France
Third NCI-EORTC Symposium on New Drugs in Cancer Therapy, October 15-17, 1981, Brussels, Belgium, European Organization for Research on Treatment of Cancer; 1981

Based on the differential template activity exhibited by DNA isolated from cancerous and healthy human or animal tissues, the Oncotest is an accurate and rapid assay for the screening of carcinogenic compounds. Thus, in the presence of all necessary components for radioactive DNA synthesis by DNA polymerase, carcinogenic compounds, antimitotic drugs (and miscellaneous compounds), at given concentrations strongly stimulate the synthesis of DNA isolated from different cancer tissues, but only slightly enhance that DNA from healthy tissues. Those carcinogens which cannot be characterized as mutagens in the Salmonella assay system, behave as carcinogens in the Oncotest. Carcinogenic potential of steroids can be shown by using the DNA from steroid hormone target tissue. There exists a common molecular mechanism through which carcinogens stimulate cancer DNA in vitro synthesis. Cancer DNAs are destabilized and in the presence of carcinogenic substances there is further DNA strand separation which accounts for the enhanced DNA synthesis. A correlation between in vitro cancer DNA synthesis, DNA strand separation and in vivo multiplication of cancerous cells can be demonstrated. Our assay system allows detection of those substances which selectively inhibit cancer DNA synthesis without affecting, in an appreciable way, that of DNA from healthy tissues. (no Refs)

9. UNSCHEDULED DNA SYNTHESIS INDUCED BY 4-AMINOAZOBENZENE, N-HYDROXY-4-AMINOAZOBENZENE, AND THEIR DERIVATIVES IN PRIMARY CULTURES OF RAT AND MOUSE HEPATOCYTES.

Watanabe HK, Hashimoto Y
Dept. Hygienic Chemistry, Pharmaceutical Inst., Tohoku Univ., Aobayama, Sendai 980, Japan
Gan; 72(6):930-936 1981

The ability of carcinogenic and non-carcinogenic aminoazo dyes to induce unscheduled DNA synthesis (UDS) in primary cultures of hepatocytes of three strains of rats and two strains of mice was examined by means of microautoradiography. Azo dyes tested were 4-aminoazobenzene (AAB) and four of its ring methoxyl (MeO) derivatives, their N-hydroxy (N-OH) derivatives, N-methyl-4-aminoazobenzene (MAB) and its N-benzoyloxy derivative, and N,N-dimethyl-4-aminoazobenzene (DAB). All carcinogenic aminoazo dyes (AAB, 3-MeO-AAB, 4'-MeO-AAB, MAB and DAB), but not the non-carcinogenic dyes (2-MeO-AAB and 2,5-diMeO-AAB), induced UDS in rat hepatocytes as well as mouse hepatocytes. N-Hydroxy derivatives of AAB and its 3-and 4'-MeO derivatives elicited higher levels of UDS than did the corresponding mother aminoazo dyes. N-OH-2,5-MeO-AAB was as inactive with rat hepatocytes as the mother dye. N-OH-2,5-diMeO-AAB, however, el icited a definite level of UDS, in contrast to the mother 2,5-diMeO-AAB. N-Benzoyloxy-MAB, a prototype compound of the ultimate carcinogenic metabolite of MAB, was as active as the mother MAB. N-OH-3-MeO-AAB induced UDS more rapidly than did 3-MeO-AAB. The UDS elicited by 3-MeO-AAB was found to end within a few hours after releasing the hepatocytes from the azo dye. (Author abstract) (33 Refs)

DNA ALTERATION AND REPAIR

MECHANISMS IN VERTEBRATES

10. HUMAN TUMOR STRAINS DEFECTIVE IN THE REPAIR OF ALKYLATED DNA FAIL TO REGENERATE RAPIDLY-SEDIMENTING NUCLEOIDS AFTER N-METHYL-N'-NITRO-N-NITROSOGUANIDINE TREATMENT.

Mattern MR, Paone RF, Day RS
Lab. Molecular Carcinogenesis, NIH, Building 37, 3C27, Bethesda, MD, 20205
Carcinogenesis; 2(11):1215-1218 1981

Upon treatment with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), human cell strains characterized as either proficient or defective both in repair of alkylation-damaged DNA and in supporting the growth of MNNG-treated adenovirus (Mer+ and Mer- phenotypes), all underwent a rapid relaxation of nucleoid DNA, as judged by sedimentation in 15-30% neutral sucrose gradients. DNA in the repair-proficient Mer+ strains (normal fibroblast and tumor) was restored to the rapidly-sedimenting (control) form within 2-4 hr after the removal of MNNG. In contrast, nucleoid DNA of the repair-deficient Mer- tumor strains remained slowly-sedimenting even after 48 hr of incubation. The delay recovery of Mer- nucleoid DNA was specific for MNNG damage, since after uv irradiation, to which Mer+ and Mer- strains are equally resistant, all cell lines tested underwent DNA relaxation within the 1st hr after irradiation (3 J/m(2)) and regenerated rapidly-sedimenting nucleoids within 4-6 hr of repair incubation. (Author abstract) (24 Refs)

11. UNSCHEDULED SYNTHESIS OF DNA AND POLY(ADP-RIBOSE) IN HUMAN FIBROBLASTS FOLLOWING DNA DAMAGE.

McCurry LS, Jacobson MK
Dept. Chemistry, North Texas State Univ., Denton, TX, 76203
J Supramol Struct Cell Biochem; 17(1):87-90 1981

The relationship between unscheduled DNA synthesis (UDS) and poly(ADP-ribose) synthesis was examined in both normal human fibroblasts (IMR90) and in cells carrying the xeroderma pigmentosum genotype (XP12BE). Cells carrying the XP gene are repair proficient for N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). XP12BE cells were found to be grossly deficient in UV-induced UDS, while the parental XP12BE heterozygote cells showed a level of UDS similar to control cells despite the fact that the rate of conversion of NAD to poly(ADP-ribose) was 1/2 that of control cells. The presence of theophylline, an inhibitor of poly(ADP-ribose)polymerase, had no appreciable effect on UDS in normal cells induced by either UV or MNNG. No direct requirement of poly(ADP-ribose) synthesis for UDS induced by either UV or MNNG has been found, but a requirement for the removal of a specific subclass of lesions or for steps in DNA repair subsequent to UDS may exist. (22 Refs)

12. REPAIR OF ETHYLNITROSOUREA-INDUCED DNA DAMAGE IN THE NEWBORN RAT. II. LOCALIZATION OF UNSCHEDULED DNA SYNTHESIS IN THE DEVELOPING RAT BRAIN.

Heyting C, Van't Veer L
Div. Chemical Carcinogenesis, Antoni van Leeuwenhoekhuis, The Netherlands Cancer Inst., 121, Plesmanlaan, 1066 CX Amsterdam, The Netherlands
Carcinogenesis; 2(11):1173-1180 1981

The developing rat brain is extremely sensitive to tumor induction by N-ethyl-N-nitrosourea (ENU). This sensitivity is ascribed to a defective repair of ENU-induced DNA damage. Because the different cell types of the developing rat brain are heterogeneous in their sensitivity to tumor induction, we decided to localize DNA-repair activities within this organ. In this paper we describe the localization of carcinogen-induced unscheduled DNA synthesis (UDS). Fresh brain slices were incubated in medium containing carcinogen and [3H]thymidine, and the incorporation of tritium was detected by autoradiography. We used two carcinogens, namely ENU (a short-patch repair agent) and the long-patch repair agent N-acetoxy-N-acetyl-2-aminofluorene (AAAF). Both carcinogens induced UDS in all nuclei in brains from 1-day-old rats. In brains from 10-day-old rats all neurons except the maturing granule cells of the cerebellum and the dentate gyrus had lost their capacity for ENU-induced UDS. In brains from 26-day-old rats no more neurons carried out ENU-induced UDS. The results obtained with AAAF resemble those obtained with ENU. However, neurons tend to lose their capacity for ENU-induced UDS earlier than that for AAAF-induced UDS: in brains from 10-day-old rats some of the neurons of the cerebral cortex and the thalamus were still capable of carrying out AAAF-induced UDS; in brains from 26-day-old rats AAAF-induced UDS could still be detected in some of the neurons of the thalamus. Those cells that are supposed to be sensitive to tumor induction by chemical carcinogens are still capable of carrying out ENU- as well as AAAF-induced UDS. Thus, the susceptibility of the different types of rat brain cells to tumor induction does not correlate with an inability to carry out carcinogen-induced UDS. (Author abstract) (33 Refs)

13. DNA REPAIR IN A UV-SENSITIVE MUTANT OF A MOUSE CELL LINE.

Sato K, Setlow RB
Div. Genetics, Natl. Inst. Radiological Sciences, 9-1, Anagawa-4-chome, Chiba-shi 260, Japan
Mutat Res; 84(2):443-455 1981

A UV-sensitive mouse cell mutant was used to examine the contribution of excision repair and post-replication repair to UV-tolerance. UV induced equal numbers of endonuclease-sensitive sites in Raji cells, mouse lymphoma L5178Y cells, and Q31 cells (a UV-sensitive mutant of L5178Y). Raji and L5178Y cells irradiated with 10 Joule/square meter removed 59% and 18% of the sites, respectively, whereas Q31 removed only 3%. Q31 cells were as efficient as the parental cells in post-replication repair. Excision-repair deficiency apparently is responsible for hypermutability and hypersensitivity to UV in Q31 cells. (26 Refs)

14. DOUBLE-STRAND BREAKS IN DNA CAUSED BY REPAIR OF DAMAGE DUE TO ULTRAVIOLET LIGHT.

Bradley MO
Merck Inst. for Therapeutic Res., West Point, PA, 19486
J Supramol Struct Cell Biochem; 16(4):337-343 1981

Induction of double strand breaks (DSB) during repair of UV light (UVL) damage was studied in human cells. UV light at doses up to 300 joule (J)/square cm (cm2) did not directly induce detectable DNA DSB in normal (IMR-90) cells irradiated and held on ice until lysis. When IMR-90 cells were irradiated with 100-300 J/cm2 of UVL at room temperature and allowed to incubate in fresh medium at 37 C, a time and dose-related increase occurred in the rate of pH 9.6 elution and therefore number of DNA DSB. DSB began to appear 3 hr after UVL and continued to increase for 51 hr. Since the cells remain attached to the dishes up to 51 hr, and all the cells ex-

clude trypan blue after 24 or 48 hr, the data suggest the DSB are not a secondary result of cell death. Using a neutral filter elution method for measuring small numbers of DSB, UVL was shown not to induce DSB in xeroderma pigmentosum (XP) complementation group A cells; the cells are unable to incise pyrimidine dimer and so cannot initiate excision repair; at the same time they are more sensitive to killing by UVL than normal cells. Thus, excision repair is implicated as a mechanism for DNA DSB formation after UVL. Repair-induced DSB may be potent lesions that lead to cytotoxicity, chromosomal aberrations, deletion mutations, and cellular transformation. (19 Refs)

15. CELLULAR DNA DAMAGE BY NITROSOCIMETIDINE: A COMPARISON WITH N-METHYL-N'-NITROSO-NITROSOGUANIDINE AND X-IRRADIATION.

Henderson EE, Basilio M, Davis RM
Fels Res. Inst., Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Chem Biol Interact; 38(1):87-98 1981

Permanently proliferating lymphoblastoid cell lines (LCLs) and normal unstimulated peripheral blood leukocytes have been used to study the effects of nitrosocimetidine (NC) on cultured human lymphoid cells. The approaches that were used to assess the cells' ability to cope with NC were: (i) determination of cell survival as measured by colony formation in microtiter plates; (ii) quantitation of DNA synthesis and DNA-repair replication by isopyknic sedimentation of DNA density labeled with 5-bromo-2-deoxyuridine (BrdU); (iii) measurement of the induction of alkali labile lesions and strand breaks by NC in 3H-labeled DNA using velocity sedimentation in alkaline sucrose. In summary, treatment with NC was fo und to inhibit both replicative DNA synthesis and colony formation in LCLs. At the molecular level, NC treatment induced alkali labile lesions in LCL DNA and elicited DNA-repair replication in proliferating LCLs as well as unstimulated lymphocytes. Considered in total, these data indicate that NC is reactive with human DNA in the cellular environment in a manner similar to methylating nitroso compounds which have been shown to be carcinogenic. The significance of these findings will be discussed. (Author abstract) (25 Refs)

16. EFFECTS OF 12-O-TETRADECANOYLPHORBOL-13-ACETATE AND MEZEREIN ON GAMMA RADIATION-INDUCED DNA REPAIR IN RESTING BOVINE LYMPHOCYTES.

Perrella FW, O'Leary P, Boutwell RK
McArdle Lab. for Cancer Res., Univ. Wisconsin, Madison, WI, 53706
Cancer Lett; 15(1):87-93 1982

The effect of the potent tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA) on gamma radiation-induced DNA repair in resting (Go) lymphocytes was studied. Lymphocytes were irradiated with appropriate doses of gamma radiation in order to introduce single-strand breaks in their DNA. The repair of DNA damage was determined by incubating irradiated (500 rad) cultures at 37 C in a water bath and at various times placing them on ice. Mezerein, a non-promoter but a co-mitogen in lymphocytes was used as a control agent. The cells were lysed immediately following irradiation on linear sucrose gradients and the distance travelled by the nucleotides was determined. The sedimentation ratio was calculated from the distance travelled by nucleoids for irradiated cells to that of unirradiated cells. It was observed that the presence of 1 uM of either TPA or mezerein in lymphocyte cultures following a 1 hr incubation did not produce a significant deviation in sedimentation behavior from dimethyl sulfoxide treated control cultures. Results indicate that neither TPA nor mezerein at 1 uM h have any degenerative effect on the integrity of the cells DNA. The percent recovery of DNA supercoil in nucleoids following 1 hr incubation of irradiated cells was 30-34% whether or not TPA or mezerein was present during recovery period. Results support the hypothesis that the tumor promoting ability of TPA is not a result of impaired repair of potentially mutagenic lesions in DNA. (20 Refs)

17. HUMAN MONOCYTES AND LYMPHOCYTES DIFFER IN THE RATE OF DNA REPAIR SYNTHESIS AND VIABILITY AFTER EXPOSURE TO NITROGEN MUSTARD.

Lewensohn R, Ringborg U
Radiumhemmet, Karolinska Hosp., Stockholm, Sweden
Acta Med Scand; 210(5):381-387 1981

Unscheduled DNA synthesis was studied in human lymphocytes and monocytes after treatment with nitrogen mustard, methyl-methane-sulfonate and ultraviolet irradiation. The unscheduled DNA synthesis was about 4x higher in monocytes than in lymphocytes after treatment with nitrogen mustard. T reatment with methyl-methane-sulfonate or ultraviolet irradiation confirmed the higher capacity for unscheduled DNA synthesis in the monocytes. When Ficoll-Isopaque-isolated mononuclear cells were exposed to various doses of nitrogen mustard and incubated for different periods, a dose- and time-dependent increase in trypan blue uptake was found. Furthermore, a corresponding dose- and time-dependent decrease was noted in 3H-uridine incorporation. Since trypan blue uptake will not enable differentiation between monocytes and lymphocytes appearing as a mixed cell population, 3H-uridine flash labeling index was studied after exposure to nitrogen mustard. There was a dose- and time-dependent decrease in 3H-uridine labeling index, suggesting a correlation between the absence of 3H-uridine incorporation and increase in trypan blue uptake. When compared to monocytes, the lymphocytes were more affected in this respect after exposure to nitrogen mustard. The possibility that differences in cytotoxic effect may be related to DNA repair mechanisms is discussed. (Author abstract) (34 Refs)

18. POSTREPLICATIVE DNA REPAIR IN UV-IRRADIATED CHINESE HAMSTER CHO CELLS.

Zhestianikov VD, Pinto RI, Tavartkiladze BA, Abramian DS
Inst. Cytology, Leningrad, USSR
Stud Biophys; 85(1):63-65 1981

Postreplication DNA repair was studied in UV-sensitive and UV-resistant clones of chinese hamster CHO cells. The most UV-sensitive clone was found to have the most pronounced DNA damage and the least effective DNA repair. (3 Refs) (In RUS)

19. INCREASED EFFICIENCY OF PHOTOREVERSAL OF UV-INDUCED DIMERS IN THE DNA OF CHICK EMBRYO FIBROBLASTS WITH POST-UV DARK TIME.

van de Merwe WP, Bronk BV
Dept. Physics, Clemson Univ., Clemson, SC, 29631
Mutat Res; 84(2):429-441 1981

Photoreversal of UV-induced dimers in DNA of chick embryo fibroblasts was assessed by monitoring the removal of UV-endonuclease-sensitive sites. Approx 1.2-1.4 dimers/10(7)

daltons of DNA (2 x 10(5) dimers/cell) were photoreactivated after a 254-nanometer (nm) UV dose followed by 6 hr dark time and a saturating dose of black light (365 nm). At least 4 hr dark time were required to saturate photoreactivation complex formation. The same black-light dose gave approx the same amount of photoreactivation for long-duration doses at low intensity as for short doses at high intensity. (27 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN BACTERIA

20. EFFECT OF THE UVRD3 MUTATION ON ULTRAVIOLET RADIATION-INDUCED DNA-REPAIR REPLICATION IN ESCHERICHIA COLI K12.

Carlson KM, Smith KC
Dept. Radiology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
Mutat Res; 84(2):257-262 1981

UV-induced DNA-repair replication was enhanced in UV-irradiated Escherichia coli K12 strain uvrD3 compared with that in the wild-type and polA1 strains. This enhanced repair replication w as reduced in the polA1 uvrDe strain and appeared to result from enhanced DNA degradation following UV irradiation. (11 Refs)

21. REPAIR AND CELL CYCLE RESPONSE IN CELLS EXPOSED TO ENVIRONMENTAL BIOHAZARDS.

Billen D, Hadden CT
Tennessee Univ., Knoxville, TN
Sci Tech Aerosp Rep; 19(22):3102 1981

Excision and recombination in the repair of damage by 8-methoxypsoralen (8-NOP) in bacillus subtilis was investigated. Topics discussed are: (1) repair of damage by psoralen plus near-UV light; (2) in vitro repair of transforming DNA; (3) photobiology of halogenated DNA; and (4) DNA repair in toluene treated Escherichia coli containing BU DNA. (Author abstract) (no Refs)

MACROMOLECULAR BINDING OF CARCINOGENS

22. QUANTITATION OF CYCLOBUTANE PYRIMIDINE DIMER FORMATION IN DOUBLE- AND SINGLE-STRANDED DNA FRAGMENTS OF DEFINED SEQUENCE.

Gordon LK, Haseltine WA
Dept. Pathology, Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
Radiat Res; 89(1):99-112 1982

Dose-response curves for the formation of cyclobutane pyrimidine dimers following irradiation with ultraviolet light were determined. It was found that the rate and extent of dimer formation was determined principally by the two nucleotides which comprised the dimer and that secondary effects were related to the identity of the two nucleotides that flank the dimer. The extent of dimer formation at a potential dimer site is a function of dose and reaches a steady-state level for all dimers at doses above 2000 Joule/square meter (m2). Rates of dimer formation and the steady-state levels are similar in single-and-double stranded DNA. Dose rates of irradiation do not affect the distribution of pyrimidine dimers over the range of 1.8-7.5 Joule/m2/sec. The quantitative data presented provide some general rules for estimating the frequency of cyclobutane pyrimidine dimer formation in heteropolymeric DNA sequences. If the pyrimidine dimer is the primary mutagenic lesion, rules could be applied to predict ultraviolet light-induced mutation frequencies in known sequences of DNA. (23 Refs)

23. PREFERENTIAL ATTACK OF MITOCHONDRIAL DNA BY AFLATOXIN B1 DURING HEPATOCARCINOGENESIS.

Niranjan BG, Bhat NK, Avadhani NG
Lab. Biochemistry, Sch. Veterinary Medicine, Univ. Pennsylvania, Philadelphia, PA, 19104
Science; 215(4528):73-75 1982

Administration of the hepatic carcinogen aflatoxin B1 to experimental animals results in covalent binding to liver mitochondrial DNA at concentrations three to four times higher than nuclear DNA. The concentration of carcinogen adducts in mitochondrial DNA remains unchanged even after 24 hr, possibly because of lack of excision repair. Similarly, mitochondrial transcription and translation remain inhibited up to 24 hr suggesting long-term effects of aflatoxin B1 on the mitochondrial genetic system . (Author abstract) (16 Refs)

24. METABOLISM AND BINDING OF BENZO(A)PYRENE AND 2-ACETYLAMINOFLUORENE BY SHORT-TERM ORGAN CULTURES OF HUMAN AND RAT BLADDER.

Moore BP, Hicks RM, Knowles MA, Redgrave S
Sch. Pathology, Middlesex Hosp. Medical Sch., Riding House St., London W1P 7LD, England
Cancer Res; 42(2):642-648 1982

The ability of organ cultures of normal human and rat bladder to metabolize the polycyclic hydrocarbon, benzo(a)pyrene (BP), and the arylamine, 2-acetylaminofluorene, has been studied. Cultures were maintained for 0 to 6 days in a chemically defined medium before incubation with [3H]BP (0.3 to 0.5 uM) or 2-[14C]acetylaminofluorene (18 to 25 uM) for 24 hr. Ethyl acetate-soluble and water-soluble metabolites were produced from both compounds by both species. The ethyl acetate extracts from [3H]BP-treated human cultures contained 9,10-dihydro-9,10-dihydroxybenzo(a)pyrene, 7,8-dihydro-7,8-dihydroxybenzo(a)pyrene, and 3-hydroxybenzo(a)pyrene. Rat bladder cultures produced similar metabolites but in slightly different proportions. Ethyl acetate-soluble products of 2-[14C]acetylaminofluorene from human cultures contained 7-hydroxy-2-acetylaminofluorine, 9-hydroxy-2-acetylaminofluorene, 2-aminofluorene, and N-hydroxy-2-acetylaminofluorene. Rat bladder cultures produced similar metabolites, but 2-aminofluorene was found in relatively higher proportion. Hydrolysis by beta-glucuronidase of the water-soluble products produced from both carcinogens gave ethyl acetate-extractable derivatives. These hydrolyzable glucuronide conjugates were relatively more abundant following metabolism of the carcinogens by the rat than by the human cultures. Covalent binding to DNA occurred with [3H]BP in both human (19.7 +-13 pmol/mg DNA) and rat cultures (22.8 +-8.6 pmol/mg DNA). As with other human tissues, considerable variation (50-fold) was observed between individuals. The results demonstrate that both human and rat bladder epithelium can metabolize known potent carcinogens and, in the case of BP, can effect covalent

binding between the products of metabolism and the urothelial cell DNA. In theory, carcinogenesis in the urinary bladder could thus be initiated by carcinogens produced or excreted in the urine without the necessity for their prior metabolism elsewhere in the body. (Author abstract) (66 Refs)

25. EFFECTS OF OXYGEN AND SULPHYDRYL-CONTAINING COMPOUNDS ON IRRADIATED TRANSFORMING DNA. PART I. ACTIONS OF DITHIOTHREITOL.

Held KD, Harrop HA, Michael BD
Dept. Therapeutic Radiology, Mayo Clinic, Rochester, MN, 55901
Int J Radiat Biol; 40(6):613-622 1981

The actions and interactions of oxygen and the sulfhydryl-containing compound dithiothreitol (DTT) upon the radiation sensitivity of the biological activity of purified Bacillus subtilis transforming DNA have been examined. It has previously been shown that the sensitivity of transforming DNA irradiated in dilute solution is less when irradiation is performed in 100% O2 than when in 100% N2, ie O2 protects transforming DNA with a dose-modifying factor of about 0.7. DTT protects transforming DNA in a manner that is dependent on DTT concentration and on gassing conditions. In O2 the DTT protection can largely be attributed to the scavenging of-0H radicals by the DTT, but in anoxia DTT exerts a further protective effect which results in an increasing oxygen enhancement ratio (oer) with increasing DDT concentration to a max oer of about 14 at 2-5 mM DTT. This additional protective effect of DTT is attributable to hydrogen atom donation from DTT to DNA radicals, thus chemically repairing the DNA. Oxygen appears to block this chemical repair reaction. (Author abstract) (23 Refs)

26. A COMPARISON OF THE CARCINOGEN-DNA ADDUCTS FORMED IN RAT LIVER IN VIVO AFTER ADMINISTRATION OF SINGLE OR MULTIPLE DOSES OF N-METHYL-4-AMINOAZOBENZENE.

Tillis DL, Straub KM, Kadlubar FF
(c/o Kadlubar) Div. Carcinogenesis, Food and Drug Admin., Environmental Protection Agency, Natl. Center Toxicology Res., Jefferson, AR, 72079
Chem Biol Interact; 38(1):15-27 1981

The compound N-methyl-4-aminoazobenzene (MAB) is believed to be metabolized in the liver to an electrophilic N-sulfonyloxy ester which binds covalently to cellular macromolecules, resulting in the induction of hepatic neoplasia. A single dose of MAB is not sufficient for complete carcinogenic activity, so we sought to identify the MAB-DNA adducts present in rat liver after multiple oral doses of [3H]MAB. The MAB was administered by intubation at a level of 0.2 mmol/kg for 1, 3 or 4 doses and animals were sacrificed at 8 hr after the last dose. Hepatic DNA was isolated by extraction and hydroxylapatite chromatography and was enzymatically hydrolyzed to MAB-mononucleoside adducts, which were quantitated by high pressure liquid chromatography (HPLC). After three doses, N2-dG, C8-dG, and an unknown adduct were detected. By four doses, these accounted for 51%, 25% and 23% of the total adducts. This data is consistent with rapid removal of the C8-dG derivative and the relative persistence of the N2-dG and the unknown adduct. The latter was shown to exhibit chromatographic and pH-dependent solvent partitioning properties that were identical to a product also present in DNA treated with the synthetic ultimate carcinogen, N-benzoyloxy-N-methyl-4-aminoazobenzene. Analysis of this adduct by field desorption mass spectrometry and, after perdeuteromethylation, by electron mass spectrometry, indicated the structure to be a deoxyadenosin-N6-yl derivative substituted through an aromatic ring of MAB. Further analysis of 270 MHz 1H-NMR spectroscopy allowed complete assignment of the MAB and adenyl resonances and was uniquely consistent with a 3-(deoxyadenosin-N6-yl)-MAB structure. Since this persistent adduct is potentially mutagenic due to possible tautomeric equilibria between the N6-amino and N6-imino structures, it may represent an initiating lesion in MAB hepatocarcinogenesis. (26 Refs)

27. AMINO ACID CONJUGATION OF N-HYDROXY-4-AMINOAZOBENZENE DYES: A POSSIBLE ACTIVATION PROCESS OF CARCINOGENIC 4-AMINOAZOBENZENE DYES TO THE ULTIMATE MUTAGENIC OR CARCINOGENIC METABOLITES.

Hashimoto Y, Degawa M, Watanabe HK, Takada M
Dept. Hygienic Chemistry, Pharmaceutical Inst., Tohoku Univ., Aobayama Sendai 980, Japan
Gan; 72(6):937-943 1981

The activation process of N-hydroxy-4-aminoazobenzene (N-HO-AAB) dyes, proximate mutagenic or carcinogenic metabolites of AAB dyes, to the ultimate mutagenic or carcinogenic metabolites was studied by the use of an amino acid conjugation (aminoacylation) system catalyzed by yeast seryl-tRNA synthetase and [3H]ATP. A potent mutagen, N-hydroxy-3-methoxy-AAB (N-OH-3-MeO-AAB), as well as a non-mutagen, N-OH-2-MeO-AAB, were equally susceptible to N-O-serine conjugation. A weak mutagen, N-OH-AAB, and a moderate mutagen, N-OH-2,5-diMeO-AAB, were also susceptible to the aminoacylation, but to a lesser extent than the 2-or 3-methoxyl homologs. In contrast, N-hydroxy-N-methyl-4-aminoazobenzene and a moderate mutagen, N-OH-4'-MeO-AAB, were not susceptible to the aminoacylation. The ability of these N-OH-AAB dyes to bind with nucleic acid after serine conjugation was proportional to the susceptibility of the dyes to serine conjugation. Serine conjugates of N-OH-AAB dyes reacted with poly G, but not with poly A, poly C, or poly U, suggesting that the azo dyes selectively bind with guanine base of nucleic acids. The susceptibility of N-OH-AAB dyes to aminoacylation was compared with the carcinogenic, mutagenic and unscheduled DNA synthesis-inducing activities of these and the mother AAB dyes. (Author abstract) (29 Refs)

28. ABERRANT AND NONRANDOM METHYLATION OF CHROMOSOMAL DNA-BINDING PROTEINS OF COLONIC EPITHELIAL CELLS BY 1,2-DIMETHYLHYDRAZINE.

Boffa LC, Gruss RJ, Allfrey VG
Rockefeller Univ., New York, NY, 10021
Cancer Res; 42(2):382-388 1982

The alkylating carcinogen 1,2-dimethylhydrazine (DMH) induces colonic tumors with high incidence. The sites of in vivo modification of target macromolecules were studied using [methyl-3H]DMH. Carcinogen binding to subcellular fractions of colonic epithelial cells was analyzed at time intervals ranging from 10 min to 36 hr, with particular emphasis on the alkylation of nuclear constituents. DMH modifies not only nucleic acids but also histones and other DNA-binding proteins in the target cells. Separation of the 3H-methylated amino acids showed aberrant methylation patterns after exposure to [3H]DMH, as compare d with methylations observed with [methyl-3H]methionine as a natural methyl group donor. DMH-modified histone H1 contained methylated lysine, arginine, and histidine residues not normally found, and other his-

tones had abnormal methylarginine contents. High-mobility-group proteins and other nuclear proteins contained methyllysine residues not normally detected. Proteins known to be associated with template-active and more accessible DNA sequences, such as the high-mobility group proteins and the multiacetylated forms of histones H3 and H4, were preferentially damaged after exposure to [3H]DMH. The result suggests that carcinogen-induced chromosomal damage is not random and may selectively affect proteins in the actively transcribing or replicating genes in the target cells. That damage affects the amino acids most likely to be involved in DNA binding. (Author abstract) (47 Refs)

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EFFECT OF CARCINOGENS ON MACROMOLECULAR SYNTHESES

29. DNA-SYNTHESIZING ACTIVITY IN MOUSE OVARY AFTER X-RAY IRRADIATION.

Martinova YS, Hadjioloff AI, Kantcheva LS
Inst. Morphology, Bulgarian Acad. Sciences, Sofia, Bulgaria
Dokl Bolg Akad Nauk; 34(7):1001-1004 1981

Effect of x-rays on DNA synthesis in ovarian cells was studied in BALB/c mice. The animals were subjected to a single irradiation with 250 or 500 rads. On days 2, 5 and 9 after irradiation mice were injected ip with 3H-thymidine, and the ovaries were examined autoradiographically. The degree of inhibition of DNA synthesis in the follicular cells depended upon the size of the follicle and the dose of irradiation. (11 Refs)

30. STIMULATION OF DNA SYNTHESIS AND CELL PROLIFERATION IN THE LIVER OF RATS FED A CHOLINE-DEVOID DIET AND THEIR SUPPRESSION BY PHENOBARBITAL.

Abanobi SE, Lombardi B, Shinozuka H
Dept. Pathology, Univ. Pittsburgh Sch. Medicine, Pittsburgh, PA, 15261
Cancer Res; 42(2):412-415 1982

Feeding of a choline-devoid (CD) diet and dietary administration of phenobarbital (PHB) are efficient promoters of liver carcinogenesis in the rat. Furthermore, inclusion of PHB in a CD diet results in a synergistic effect, inasmuch as the promoting action of their combination is greater than the sum of those exerted by either agent alone. To investigate the mechanism(s) of action of the two promoters, liver DNA synthesis and liver cell proliferation were studied in rats fed a CD diet, a choline-supplmented diet, or the same diets to which 0.06% PHB was added. DNA synthesis was determined by [3H]thymidine incorporation into DNA and autoradiography, and cell proliferation was determined by mitosis counts. Feeding the CD diet caused an increase of both DNA synthesis and cell proliferation over those present in rats fed the choline-supplemented diet. Inclusion of PHB in the CD diet, on the other hand, inhibited DNA synthesi s and cell proliferation. These results indicate that stimulation of cell proliferation per se may not be a sufficient condition for an agent to act as a promoter of liver carcinogenesis. (Author abstract) (32 Refs)

31. ELEVATED LEVELS OF ORNITHINE DECARBOXYLASE AND POLYAMINES IN THE KIDNEYS OF ESTRADIOL-TREATED MALE HAMSTERS.

Nawata H, Yamamoto RS, Poirier LA
Nutrition and Metabolism Section, Lab. Carcinogen Metabolism, NCI, Bethesda, MD, 20205
Carcinogenesis; 2(11):1207-1211 1981

The effects of 17 beta-estradiol (E2) on the levels of ornithine decarboxylase (ODC), S-adenosylmethionine decarboxylase (SAMDC), and of the polyamines putrescine, spermidine and spermine in the kidneys of castrated male hamsters were determined. The ip injection of E2 into male hamsters led to renal ODC levels three times above the control levels 6-12
binding to renal estradiol receptor sites in vitro. The hamster kidney levels of the polyamines putrescine, spermidine and spermine all declined during the 180-day experimental period. A single ip injection of E2 led to a 70% increase in renal SAMDC activity 12 hr after treatment. However, the administration of E2 for 180-270 days was without effect on the normal age-dependent decline in SAMDC levels noted in kidneys. These results indicate that, like other carcinogens and promoters, E2 increases the levels of ODC and of polyamines in its target tissue and that the rise in ODC is mediated by a specific estradiol-binding protein. (Author abstract) (30 Refs)

REVIEWS

32. ANTINEOPLASTIC AGENTS.

Struck RF
Southern Res. Inst., Birmingham, AL, 35255
Annu Rep Med Chem; 16:137-147 1981

Publications and reports on various aspects of anticancer drug development are reviewed. Alkylating agents, pyrimidine, purine and folate antagonists, anthracyclines, natural products, semi-synthetics, and miscellaneous synthetic agents are presented. A quantitative structure-activity relationship for 90 nitrosoureas was formulated, and 1-(2-chloroethyl)-1-nitroso-3-(methyl enecarboxamido)urea, 2-3-(2-chloroethyl)-3-nitrosoureido-ethylmethane sulfonate, and chlorozotocin were effective against 7,12-dimethyl-benz(a)anthracene-induced mammary cancer. Selective toxicity of mitomycin suggests that such bioreductive alkylating agents have the potential to attack selectively the chemotherapeutically resistant hypoxic cell component of solid tumors. Clinical demonstration that cross-resistance between mustard-type alkylating agents does not exist in some tumors was found when cyclophosphamide- resistant breast cancer responded to treatment with peptichemio. Methotrexate polyglutamates, which are formed in human tumor cells and bind to dihydrofolate reductase, may be selectively retained in cells and may be important of duration of action and cytotoxicity of methotrexate in human solid tumors. Studies of the interaction between adriamycin and phospholipids indicate similar association constants for such complexes and DNA complexes. Mitotic inhibitors ansamitocins demonstrated high activity against experimental tumors in vivo and are possible alternatives to vinca alkaloids. Three intercalating 7H-pyrido(4,3-c)carbazole dimers with rigid bis(ethyl-piperidyl)

chains were highly active against LL. Mutagenic and antitumor activity of methanesulfonamide derivatives can be separated in the series by appropriate choice of substituent and adjustment of overall lipophilic/hydrophilic balance. Seventy percent complete regression rate was obtained with penberol in a limited number of patients with stage III and IV ovarian carcinoma. (204 Refs)

33. MUTAGENESIS AND CARCINOGENESIS TESTING IN VITRO.

Casto BC
Northrop Services, Incorporated, P.O. Box 12313, Research Triangle Park, NC, 27709
Biotechnol Bioeng; 23(12):2659-2671 1981

Assays of mutagenicity currently being implemented in mammalian cells are reviewed along with a brief description of the methodology, advantages, and disadvantages, and correlation with known in vivo activity. Mammalian cell transformation assays discussed are mass culture, clonal assays, focus assays and soft agar assays. Mammalian cell mutation assays in vitro utilize both cell strains and continuous cell lines. Both established in vitro systems and systems being developed are outlined, as are in vivo-in vitro systems. Parameters associated with in vitro cell transformation and selection of drug-resistant phenotypes for detection of mutation in mammalian cells are outlined. The close association between mutagenic and carcinogenic activity for a large number of chemical compounds has focused attention on interaction between chemical carcinogens and cellular DNA. Studies on DNA fragmentation and DNA repair (unscheduled DNA synthesis) are briefly discussed. (44 Refs)

34. CURRENT CONCEPTS AND CONTROVERSIES IN CHEMICAL CARCINOGENESIS.

Weinstein IB
Div. Environmental Sciences, Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 17(2):99-120 1981

Fundamental research at the cellular and molecular levels on mechanisms of action of chemical carcinogenesis and applied aspects and the concept of 'molecular epidemiology' of cancer are reviewed. The action of initiating agents and their metabolism and covalent binding to macromolecules is discussed under the following headings: metabolic activation, carcinogen potency, structures of carc inogen-DNA adducts, conformational changes in DNA, carcinogen modification of mitochondrial DNA, DNA repair, and carcinogen-DNA modification and mechanism of initiation. Tumor promotion and multifactor interactions are discussed in relation to two-stage skin carcinogenesis. Numerous effects elicited by phorbol ester tumor promotors, particularly 12-O-tetradecanoyl-phorbol-13-acetate, are classified into three categories: mimicry of transformation, modulation of differentiation, and membrane effects. Also considered in relation to phorbol ester tumor promotors, tumor promotion, and multifactor interactions are phorboid receptors, ion flux, possible role of kinases, chromosomal effects and activated oxygen, and chemical-viral interactions. The tumor-promoting activity of polycyclic aromatic hydrocarbons is discussed. A unified theory of tumor initiation and promotion is presented. Molecular epidemiology and cancer prevention are discussed with regard to limitations of current approaches and molecular cancer epidemiology. (94 Refs)

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As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. ETHYLENE OXIDE (ETO): EVIDENCE OF CARCINOGENICITY.
Coene RF
National Inst. for Occupational Safety and Health, Cincinnati, OH
Vet Hum Toxicol; 23(6):439-443 1981

DIETARY FACTORS IN CARCINOGENESIS

2. NUTRITIONAL ASPECTS OF CANCER PREVENTION: AN OVERVIEW.
Silverman J
American Health Foundation, Naylor Dana Inst Disease Prevention, Valhalla, NY, 10595
J Am Vet Med Assoc; 179(12):1404-1409 1981

3. FORMATION OF N-NITROSO COMPOUNDS IN FOODS.
Gray JI
Dept. Food Science and Human Nutrition, Michigan State Univ., East Lansing, MI, 48824
ACS Symp Ser; 174():165-180 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

4. LYMPHOMAS AND LEUKAEMIAS. PART 2: TROPICAL AMERICA.
Jimenez E
Hospital Nacional de Ninos 'Dr. Carlos Saenz Herrera', Apartado 1654, San Jose, Costa Rica
Clin Haematol; 10(3):894-915 1981

5. LYMPHOMAS AND LEUKAEMIAS. PART 1: TROPICAL AFRICA.
Olweny CL
Uganda Cancer Inst., P.O. Box 3935, Kampala, Uganda
Clin Haematol; 10(3):873-893 1981

6. MALIGNANT MELANOMA.
Creagan ET
Div. Medical Oncology, Mayo Clinic, Rochester, MN, 55905
Compr Ther; 7(12):36-44 1981

7. MELANOTIC TUMORS OF THE UVEA AND RETINA.
Schmitt H
Universitats-Augenklinik, Theodor-Stern-Kai 7, D-6000 Frankfurt am Main, W. Germany
Med Klin; 76(24):672-675 1981
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CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

8. THE NATURAL HISTORY OF CARCINOGENESIS: IMPLICATIONS OF EXPERIMENTAL CARCINOGENESIS IN THE GENESIS OF HUMAN CANCER.
Pitot HC, Goldsworthy T, Moran S
McArdle Lab. for Cancer Res., Dept. Oncology, Medical Sch., Univ. Wisconsin, Madison, WI, 53706
J Supramol Struct Cell Biochem; 17(2):133-146 1981

9. CURRENT CONCEPTS AND CONTROVERSIES IN CHEMICAL CARCINOGENESIS.
Weinstein IB
Div. Environmental Sciences, Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 17(2):99-120 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

10. BURKITT'S LYMPHOMA.
Ambrus JL, Ambrus CM
Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Med; 12(6):385-413 1981

11. PRIMARY HEPATIC CARCINOMA.
Iosquin CJ
Catedra de Medicina Interna A, Facultad de Ciencas Medicas, La Plata, Argentina
Rev Fac Cienc Med La Plata; 4(2):27-31 1981
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METHODOLOGY IN CARCINOGENESIS RESEARCH

12. MUTAGENESIS AND CARCINOGENESIS TESTING IN VITRO.
Casto BC
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Biotechnol Bioeng; 23(12):2659-2671 1981

OTHER REVIEWS IN CARCINOGENESIS

13. CANCER IN THE YEAR 2000. A REVIEW.
Saxen E
Suomen Syoparekisteri, Linsankatu 21 B, 00170 Helsinki 17, Finland
Duodecim; 97(20):1708-1716 1981
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Macromolecular Alteration and Repair

SERIES CK11 No. 82/06

JUNE, 1982

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BIOLOGICAL ASPECTS OF DNA

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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ALTERATION AND REPAIR IN RELATION TO CARCINOGENICITY

1. DNA DAMAGE AND ITS REPAIR IN HUMAN NORMAL OR XERODERMA PIGMENTOSUM FIBROBLASTS TREATED WITH 4-NITROQUINOLINE 1-OXIDE OR ITS 3-METHYL DERIVATIVE.

Mirzayans R, Waters R
Dept. Genetics, Univ. Coll. Swansea, Singleton Park, Swansea SA2 8PP, England
Carcinogenesis; 2(12):1359-1362 1981

Normal human or excision deficient xeroderma pigmentosum (XP) fibroblasts were exposed to either the potent carcinogen 4-nitroquinoline 1-oxide (4NQO) or the weaker acting 3 methyl derivat ive of this compound. The inhibition of cell growth, DNA damage and DNA repair were then monitored in these cells. The data indicate that the modification of 4NQO by methylation actually changes the type and amount of DNA damage induced by this carcinogen. More specifically, the methylation of 4NQO at the three position prevented the formation of 4NQO induced DNA adducts manifesting themselves as alkaline stable lesions whose repair was cytosine arabinoside inhibitable in normal cells, but defective in excision deficient XP cells. Alkaline labile lesions induced by 4NQO which are repairable in the above XP cells were still induced by the 3 methyl derivative but a lower frequency on an equimolar basis. (Author abstract) (13 Refs)

2. INTERACTION OF HUMAN AND CHICK DNA REPAIR FUNCTIONS IN UV-IRRADIATED XERODERMA PIGMENTOSUM-CHICK ERYTHROCYTE HETEROKARYONS.

Bootsma D, Keijzer W, Van Der Veer E, Rainaldi G, De Weerd-Kastelein EA
Dept. Cell Biology and Genetics, Erasmus Univ. Rotterdam, 3000 DR Rotterdam, The Netherlands
Exp Cell Res; 137(1):181-189 1982

Fusion of chick erythrocytes with human primary fibroblasts results in the formation of heterokaryons in which the inactive chick nuclei become reactivated. The expression of chick DNA repair functions was investigated by the analysis of the DNA repair capacity after exposure to ultraviolet (UV) irradiation of such heterokaryons obtained after fusion of chick erythrocytes with normal human or xeroderma pigmentosum (XP) cells of complementation groups A, B, C, and D. Unscheduled DNA synthesis (UDS) in normal human nuclei in these heterokaryons is suppressed during the first 2-4 days after fusion. The extent and duration of this suppression is positively correlated with the number of chick nuclei in the heterokaryons. Suppression is absent in heterokaryons obtained after fusion of chicken embryonic fibroblasts with XP cells (complementation group A and C). Restoration of DNA repair synthesis is found after fusion in XP nuclei of all complementation groups studied. It occurs rapidly in XP group A nuclei, starting one day after fusion and reaching near normal human levels after 5-8 days. In nuclei of the B, C and D group increased levels of UDS are found 5 days after fusion. At 8 days after fusion the UDS level is about 50% of that found in normal human nuclei. The pattern of UDS observed in the chick nuclei parallels that of the human counterpart in the fusion. A fast complementation pattern is also observed in chick fibroblast-XP group. A heterokaryons resulting within 24 hr in a UDS level comparable with that in chick fibroblast-normal human heterokaryons. In heterokaryons obtained after fusion of chick fibroblasts with XP group C cells UDS remains at the level of chick cells. These data suggest that reactivation of chick erythrocyte nuclei results in expression of r epair functions which are able to complement the defects in the XP complementation groups A, B, C and D. (Author abstract) (15 Refs)

3. REJOINING OF DNA DOUBLE-STRAND BREAKS IN HUMAN FIBROBLASTS AND ITS IMPAIRMENT IN ONE ATAXIA TELANGIECTASIA AND TWO FAŃCONI STRAINS.

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J Supramol Struct Cell Biochem; 17(4):369-376 1981

Repair of DNA double-strand breaks (DSB) in fibroblasts from normal individuals and patients with ataxia telangiectasia (AT) or Fanconi's anemia (FA) was studied. Cell strains tested included 'Munich' from a normal child, 'Berlin' from a normal adult, AT2BE, AT3BI, and AT5BI from patients with AT, and FA CRL 1196, FA Buse, FA 1424, and FA 3557 from patients with FA. Cell cultures were exposed to gamma-radiation (33 Gray/min for 1.5 min) and incubated at 37 C under aerobic conditions; cells not incubated were irradiated at 0 C. DNA DSB were analyzed by neutral filter elution. The lowest dose of radiation producing measurable DSB was 5 Gray, which produced one DSB/3.2 daltons DNA. At 37 C fibroblasts from normal individuals (adult and child) repaired approx 50% of DSB resulting from 50 Gray within 3 min; after 30 min 90% of DSB were repaired. DSB were repaired by a fast repair mechanism and a slow mechanism. Cells from strain AT2BE showed defective fast and slow repair mechanisms. After long incubation times AT2BE cells retained 4-6% more DSB than normal cells. AT3BI and AT5BI cells showed normal repair mechanisms. FA3557 and FA1424 showed defective fast and slow repair mechanisms. FA CRL 1196 and FA Buse showed normal repair mechanisms. Defective DSB repair is apparently the result of deficient enzyme activity. (20 Refs)

4. THE RESPONSE OF ATAXIA TELANGIECTASIA CELLS TO NEOCARZINOSTATIN (MEETING ABSTRACT).

Tatsumi K, Kurihara T, Inoue M
Department of Medicine, Kanazawa Medical University, Ishikawa, Japan
Proceedings of the Japanese Cancer Association 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The autosomal recessive disorder, ataxia telangiectasia (AT) is characterized by cellular sensitivity of ionizing radiation. The antitumor antibiotic neocarzinostatin (NCS) produces apurinic/apyrimidinic (AP) sites and strand breaks in cellular DNA and lowers the cellular concentration of NAD. Compared with normal fibroblast cells, three AT cell strains (AT3BI, AT5BI and AT10S) exhibited diminished survival after treatment with NCS for 1 hr as assayed by posttreatment colony-forming ability. A possible DNA repair defect(s) may be specific for AP sites and/or DNA strand breaks. (no Refs)

5. X-RAY INDUCED CHROMOSOME ABERRATIONS IN DOWN LYMPHOCYTES: AN EXPLANATION OF THEI R INCREASED SENSITIVITY.

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Environ Mutagen; 3(1):85-89 1981

Association between altered repair of radiation-induced damage in lymphocytes from two individuals with Down syndrome (trisomy 21) compared with normal cells, and the involvement of the association in increasing chromosome aberration frequencies, were studied. Aberration frequencies in normal and Down lymphocytes were compared following x-irradiation and postirradiation incubation with cytosine arabinoside (ara-C), 5 x 10(-5) M, for 0, 0.5, 1 or 2 hr. Unstimulated Down lymphocytes are more sensitive to the induction of dicentric and ring aberrations by x-rays than normal lymphocytes. X-irradiated cells incubated with ara-C exhibited large increases in aberration frequencies which were proportional to length of exposure to ara-C. Results suggest that the initiation of the repair of damage which is converted into chromosome aberrations is more rapid in Down cells than in normal cells. This could be explained if the total amount of DNA damage which can be converted int aberrations is the same in both cell types but the repair is more rapid in Down cells. Results explain the increased sensitivity of unstimulated lymphocytes from individuals with Down syndrome to the induction of dicentrics by x-rays. The more rapid repair of Down cells results in a higher probability of producing chromosome aberrations and higher aberration frequencies in Down than normal cells. (5 Refs)

6. DECREASED RATE OF BENZO(A)PYRENE-INDUCED SISTER CHROMATID EXCHANGE IN FIBROBLAST CULTURES FROM PATIENTS WITH LUNG CANCER.

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J Cancer Res Clin Oncol; 102(2):169-175 1981

Fibroblast cultures from 29 lung cancer patients including 9 familial cases and from 25 healthy controls were investigated. We studied the benzpyrene-induced sister chromatid exchange (SCE) following incubation in the presence of 150 nM benzo(a)pyrene and found spontaneously increased SCE values in the patients' cells but a reduced response to benzpyrene as compared to the control cultures. The benzpyrene-induced SCE was positively correlated with both benzpyrene metabolism and DNA adducts in normal control cells but not in the patients' cells. The ratio of benzpyrene DNA adducts and benzpyrene-induced rate of SCE calculated for the individual cell strains exhibited a bimodal distribution with patients' cells, but not with control cells. We speculate that the described differences between patients' and control fibroblasts might reflect a genetic predisposition to the development of lung cancer in about one half of the patients tested. (Author abstract) (10 Refs)

7. DNA RADIOSENSITIVITY IN CARCINOMA OF THE HUMAN CERVIX.

Ono T, Okada S, Iwata M, Ishii H, Hosokawa T
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Strahlentherapie; 157(1):33-36 1981

The radiosensitivity of DNA in human cervix carcinomas was examined by using alkaline sucrose gradient centrifugation to measure radiation-induced single-strand breaks. The DNA strand-break efficiencies observed in DNA of 18 specimens fell into two distinct groups, radiosensitive and radioresistant. The difference in DNA radiosensitivity may be correlated with the pathological classifications of the carcinomas. (Author abstract) (14 Refs)

8. DYSKERATOSIS CONGENITA: SURVIVAL, SISTER-CHROMATID EXCHANGE AND REPAIR FOLLOWING TREATMENTS WITH CROSSLINKING AGENTS.

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Mutat Res; 103(3-6):327-332 1982

Normal human fibroblasts NHSF 46 and dyskeratosis congenita (DC) strains DC1KO, DC2K0, and DC1JTO were cultured in Eagle's essential minimal medium, and the lethal effects of the cross-linking agents mitomycin C (MC:0.1-0.5 mg/ml) and 4,5',8-trimethylpsoralen (TMP:10 7-6 1 M) + near-UV light were determined. All DC-strain cells exhibited the same resistance to killing as normal cells for both treatments. Linear SCE induction coefficients were the same after treatment of the four cell lines with both agents, and a baseline SCE frequency of about 5/cell was observed for all strains used. DNA repair processes in DC1K0 cells and NHSF46 cells were shown to be similar by sedimentation velocity analysis. These results may be used to differentiate DC cells from those of Fanconi's anemia, a condition sometimes confused with DC, but in which chromosomes are typically unstable. (16 Refs)

BIOLOGICAL ASPECTS OF DNA ALTERATION AND REPAIR IN RELATION TO MUTAGENICITY

9. ROLE OF DNA REPAIR IN MUTAGENESIS OF CHINESE HAMSTER OVARY CELLS BY 7-BROMOMETHYLBENZ[A]ANTHRACENE.

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Proc Natl Acad Sci USA; 79(2):534-538 1982

The role of DNA repair in mutagenesis was studied in normal, repair-proficient Chinese hamster ovary cells and in two mutant strains that are deficient in excision repair. By using the mutagen 7-bromomethylbenz[a]anthracene (7-BrMeBA) and the technique of alkaline elution of DNA, the mutants were found to be defective at or before the incision step of excision repair. Dose-responses were determined for cell killing, mutation induction at three loci, and sister chromatid exchanges over a survival range of 1.0-0.1 after 7-BrMeBA treatment. The mutants were five-fold more sensitive to k illing than were the normal cells, but the degree of hypersensitivity to mutation induction varied depending on the mutant strain, the genetic marker, and the dose of mutagen. In each instance, the dose-response curve for mutations was essentially linear in the repair-deficient cells. In the normal cells, however, the curves for induced resistance to thioguanine and azaadenine were complex and were curvilinear with increasing slope at low doses. This behavior may be attributable to saturation of the excision repair system. No difference was seen in the efficiency of inducing ouabain-resistant mutations in the repair-de-

ficient cells compared to the normal cells, indicating a qualitatively different behavior of this marker. These results are consistent with excision repair of 7-BrMeBA damage being error-free in Chinese hamster ovary cells. Sister chromatid exchange, another manifestation of DNA damage, also was induced with greater efficiency in the repair-deficient cells. (Author abstract) (34 Refs)

10. MUTAGENICITY OF 4-CHLOROMETHYLBIPHENYL IN REPAIR-DEFICIENT STRAINS OF SALMONELLA TYPHIMURIUM.

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Mutat Res; 100(1-4):75-79 1982

The mutagenic activity of 4-chloromethylbiphenyl (4CMB) was examined in a series of repair deficient derivatives of Salmonella typhimurium LT2 using the fluctuation test. 4CMB was mutagenic to frameshift tester strains at 0.01-50 ug/ml, except in genetic backgrounds; no mutagenicity was observed in base-pair substitution tester strains at the dose levels used, except in the presence of the plasmid pKM101. Thus 4CMB appears to be primarily active as a frameshift mutagen. A much greater effect was seen in the excision-deficient strain TA1533 than in the repair wild-type strain D3052, suggesting that 4CMB forms an excisable DNA adduct. Increased cellular permeability resulting from the 'deep rough' (rfa) mutation led to greater mutation production by 4CMB, as can be seen by comparison of results for strains TA1533 and TA1538 which are isogenic except for the rfa mutation in TA1538. Strain TS27, which carries the recA allele and is completely deficient in recombination and error-prone repair, was almost as sensitive to 4CMB mutation as D3052; such a result suggests that a substantial proportion of the frameshift activity of 4CMB is independent of rec-lex function, consistent with the finding that the plasmid pKM101 has no observable effect on frameshift mutation by 4CMB and strains TA98 and TA1538 are equally sensitive to 4CMB mutation. The mechanism of 4CMB mutagenesis is discussed. (14 Refs)

11. COMPARATIVE EVALUATION OF DIFFERENT PAIRS OF DNA REPAIR-DEFICIENT AND DNA REPAIR-PROFICIENT BACTERIAL TESTER STRAINS FOR RAPID DETECTION OF CHEMICAL MUTAGENS AND CARCINOGENS.

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Mutat Res; 97(1):1-18 1982

Carcinogenic and noncarcinogenic compounds, including antibiotics, polycyclic aromatics, aromatic amines, alkyl halides, esters, epoxide carbamates and related compounds, nitroaromatics and heterocyclics, nitroso compounds, hydrazine compounds, azo compounds, and other bioactive agents, were tested for mutagenicity with the agar incorporation test (AT) and the spot test (ST). Two paired (DNA repair proficient/repair deficient) Bacillus subtilis systems, H17/M45 and HLL3g/HJ-15, were used, and the repair-proficient Escherichia coli A1157 strain was paired with the repair-deficient strains JC2921, JC2926, JC5519, and JC5547. Results were compared with reported carcinogenicity and/or Ames test mutagenicity, or in some cases with Ames Salmonella (TA1535, TA1537, TA1538, TA98, TA100) assays reported here for the first time. E coli systems yielded a high number of 'no result' findings as well as many false-positive outcomes. B subtilis systems were generally reliable indicators of carcinogenicity, especially if both AT and ST were used. The bacterial DNA-repair tests agreed more often with the Ames test than with carcinogenicity results. When both pairs of B subtilis strains were combined with the Ames assay, excess false-positives did not appear, whereas the number of false-negative findings with carcinogens was reduced. The slightly increased probability of uncovering a suspected carcinogen does not seem to justify inclusion of the extra tests in a battery, except when working with chemicals of classes in which the Ames test is known to be less sensitive. (59 Refs)

12. METABOLIC ACTIVATION OF CARCINOGENS IN THE SALMONELLA MUTAGENICITY ASSAY BY HAMSTER AND RAT LIVER S-9 PREPARATIONS.

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Chemical Carcinogenesis Program, Fredrick Cancer Res. Center, Frederick, MD, 2170.
Environ Mutagen; 3(1):71-84 1981

In the Salmonella mutagenicity assay, mutagenicity of the known carcinogens 2-acetylaminofluorene (AAF), 2-aminoanthracene (AA), 3-methylcholanthrene (MCA), benzo(a)pyrene (BP), and diethylnitrosamine (DEN) were directly compared using either uninduced or phenobarbital (PB)- or Aroclor (AC)-induced liver S-9 preparations from both male and female hamsters and rats. Effects of different concentrations of the S-9 protein were studied. Mutagenicity data were compared with the aryl hydrocarbon hydroxylase (AHH) and BP-4,5-epoxide hydrase (EH) activities of the liver S-9 preparations, and the levels of binding of BP metabolites to DNA were measured. The preparations from hamster liver were consistently more effective than those from rat liver for the activation of AAF, AA (except for AC-induced preparations), MCA, and DEN to their mutagenic forms. Induced preparations from rats were more active than thos e from hamsters when using BP. With the aromatic amines (AAF and AA), a partial inhibition of mutagenicity occurred at the highest protein concentrations tested. Inverse relationship was observed with BP between protein concentration and number of revertants occurring in the presence of the preparation from PB- and AC-induced male and female rats. Relative order of activities of AHH and EH in preparations was AC-induced greater than PB-induced greater than uninduced. An exception was the liver S-9 preparation from AC-induced female rats, which induced no EH activity. Levels of binding of the metabolites of tritiated BP to calf thymus DNA were correlated with AHH levels except in the case of the preparation from PB-induced female rats, in which no binding was detected. (31 Refs)

13. CHEMICALLY-INDUCED UNSCHEDULED DNA SYNTHESIS IN PRIMARY RAT HEPATOCYTE CULTURES: A COMPARISON WITH BACTERIAL MUTAGENICITY USING 218 COMPOUNDS.

Probst GS, McMahon RE, Hill LE, Thompson CZ, Epp JK, Neal SB
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Environ Mutagen; 3(1):11-32 1981

Hepatocyte primary culture (HPC)-DNA repair test using a relatively large number of compounds representing a wide variety of chemical classes is discussed. Over 200 compounds were tested for induction of unscheduled DNA synthesis (UDS) and the results were correlated with bacterial mutagenicity using a modified Ames test. A positive response was seen in both systems with many procarcinogens and ultimate car-

cinogens while compounds believed to be noncarcinogens were inactive. Recognized carcinogens/mutagens were readily detected by the two systems. Structurally realted noncarcinogens produced negative results in both systems. The modified Ames test and the HPC-UDS repair test were sensitive to compounds capable of interacting with DNA, and represent acceptable tests for genotoxic substances. The induction of UDS in hepatocytes showed good correlation with bacterial mutagenesis in response to polycyclic aromatic hydrocarbons, aromatic amines, biphenyls, nitrosamines, carbamates, azo-compounds, acridines, halogenated compounds, nitrosoureas, quinolines, pyridines, purines, pyrimidines, esters, and carbamates. Nitrocompounds although active in bacteria, were poor inducers of UDS. Results support the complementary and confirmatory nature of the tests for genotoxic chemicals and indicate the usefulness of the hepatocyte UDS system as a component in a battery of short-term predictive tests for mutagens/carcinogens. (45 Refs)

14. THE MUTAGENICITY OF DIALKYLAMINOALKYL CHLORIDES IN A BATTERY OF SHORT-TERM ASSAYS.

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Environ Mutagen; 3(1):33-43 1981

A battery of four short-term tests was employed in the study of dialkylaminoalky l chlorides (DAAC). All DAAC compounds were screened by the concentration gradient technique for their ability to produce an increase in revertants in any of 10 bacterial strains used in the assay. The concentration gradient results were supplemented by determination of concentration-response relationships (Ames test) in the appropriate tester strains. Two additional tests performed were for chemically induced DNA repair in rat hepatocyte primary cultures (HPC-DNA repair) and for mutation at the thymidine kinase locus in the L5178Y mouse lymphoma cell. There was good correlation between results of the gradient plate test and the Ames test. DAAC were active in all test systems. Relative mutagenic potencies of the ethyl chlorides were similar in the bacterial tests and the L5178Y cell assay. Dialkylaminopropyl chlorides (DAAP) were weakly mutagenic in two Salmonella strains but were inactive in other test systems. Results with dialkylaminoethyl compounds suggest that if these agents which can form the aziridinium ion were evaluated in in vivo tests some would be found to be carcinogenic. Data on DAAP indicate that they have a low carcinogenic potential. (9 Refs)

15. UKEMS TRIAL COMPOUNDS: INDUCTION OF UNSCHEDULED DNA SYNTHESIS IN HELA S3 CELLS.

Barrett RH
Res. Dept., Boots Co. Ltd., Pennyfoot St., Nottingham NG2 3AA, England
Mutat Res; 100(1-4):207-209 1982

Significant increases in unscheduled DNA synthesis (UDS) in HeLa S3 cells were induced at 4-chloromethylbiphenyl (4CMB) dose levels of 10(-4) and 10(-5) M in the absence and 10(-5) M in the presence of S9 mix. 4-Hydroxymethylbiphenyl (4HMB) showed no evidence of UDS induction at dose levels up to 10(-3) M; cytotoxicity was evident at this concentration. BC slightly elevated UDS at 10(-4) M in the absence of S9 mix. The results indicated carcinogenicity of 4CMB and 4HMB but did not agree with previous findings on tumorigenicity of BC in rats. (9 Refs)

16. DETECTION OF CHEMICAL CARCINOGENS BY ASSAY OF UNSCHEDULED DNA SYNTHESIS IN RAT TRACHEAL EPITHELIUM IN SHORT-TERM ORGAN CULTURE.

Ide F, Ishikawa T, Takayama S
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J Cancer Res Clin Oncol; 102(2):115-126 1981

A short-term organ culture of rat tracheal epithelium was used to detect the ability of 53 chemicals to induce UDS. In this system all direct-acting compounds (ultimate or proximate carcinogens) tested induced UDS. Of 24 compounds requiring metabolism (procarcinogens), nine induced UDS, viz, 4NQO, AF-2, BP, DMN, DEN, and NP. Urethane, AAF, and 2,7-AAF induced very slight UDS. 3-Methyl-4NQO for which carcinogenicity data is incomplete was positive in our system. Among the cancer chemotherapeutic agents tested only mitomycin C induced UDS. MC and DMBA, which are known to induce cancer of respiratory organs in experimental animals, and DAB, aflatoxin B1 and Trp-P-1, which are strong carcinogens in the liver, did not induce UDS within 2 hr. With the longer exposure (24 hr), these carcinogens also failed to elicit UDS. All the carcinogens that induce UDS showed clear dose-dependent effects. No non-carcinogens tested induced UDS. These results suggested that this system should be useful for screening environmental chemicals suspected of damaging DNA of the respiratory organ on the basis of organotropic effects of UDS induction in cultured rat tracheal epithelium. (Author abstract) (54 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN VERTEBRATES

17. RADIOIMMUNE ASSAY OF INDUCTION AND REMOVAL OF UV LESIONS IN TOTAL AND STAPHYLOCOCCAL NUCLEASE-RESISTANT DNA OF MAMMALIAN CHROMATIN.

McConlogue LC, Ward JF, Lewis HL, Norman A
Dept. Microbiology and Immunology, Univ. California, San Francisco, CA, 94143
Radiat Res; 89(2):381-395 1982

A direct lesion radioimmunoassay was used to measure induction and repair removal of UV lesions in total DNA (DNAt) and Staphylococcal nuclease-resistant DNA (DNAr). UV lesion induction in DNAr of HeLa and CHO cells was about 80% of that in DNAt. The two- to four-fold difference in repair synthesis observed in these DNAs cannot be accounted for by this result. The equal amounts of lesions per unit DNA in DNAr and DNAt of HeLa cells at 6 hr of repair induction can be explained by either the lower rate of lesion removal in staphylococcal nuclease-resistant DNA or complete nucleosomal rearrangement with respect to UV lesions during repair. (35 Refs)

18. CHRONIC OR ACUTE ADMINISTRATION OF VARIOUS DIALKYLNITROSAMINES ENHANCES THE REMOVAL OF O6-METHYLGUANINE FROM RAT LIVER DNA IN VIVO.

Margison GP
Paterson Lab., Christie Hosp., Holt Radium Inst., Manchester M20 9BX, England
Chem Biol Interact; 38(2):189-201 1982

The effect of pretreatment of rats with various symmetrical dialkylnitrosamines on the repair of O6-methylguanine produced in liver DNA by a low dose of [14C]dimethylnitrosamine (DMN) has been examined. DMN, diethylnitrosamine (DEN), dipropylnitrosamine (DPN) or dibutylnitrosamine (DBN) were administered to rats for 14 consecutive weekdays at a daily dose of 5% of the LD50. Animals were given [14C]DMN 24 hr after the last dose and were killed 6 hr later. DNA was extracted from the liver and analyzed for methylpurine content after mild acid hydrolysis and Sephadex G-10 chromatography. While the amounts of 3-methyladenine and 7-methylguanine were only slightly different from controls, the amounts of O6-methylguanine in the DNA of the dialkylnitrosamine pretreated rats were about 30% of those in control rats, indicating a considerable increase in the capacity to repair this base. Liver ribosomal RNA from control and dialkylnitrosamine pretreated rats contained closely similar amounts of O6-methylguanine suggesting that the induced enzyme system does not act on this base in ribosomal RNA in vivo. Pretreatment with these dialkylnitrosamines also enhanced the repair of O6-methylguanine in liver DNA when they were given as a single dose (50% of the LD50) either 3 or 7 days before the [14C]DMN. In addition, single low doses of DMN or DEN (5% of the LD50) given either 1 or 6 days before [14C]DMN increased O6-methylguanine repair and the magnitude of the effect after DEN was similar to that produced by the other pretreatment schedules. The possible mechanism(s) of the induction of O6-methylguanine repair and its relation to hepatotoxicity, DNA alkylation, carcinogenesis and the adaptive response in Escherichia coli are discussed. (Author abstract) (42 Refs)

19. DNA DAMAGE INDUCED BY THE ANTIHISTAMINIC DRUG METHAPYRILENE HYDROCHLORIDE.

Althaus FR, Lawrence SD, Sattler GL, Pitot HC
McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706
Mutat Res; 103(3-6):213-218 1982

Methapyrilene hydrochloride (MH) added to the medium stimulated DNA-repair synthesis in cultured hepatocytes from adult male Holtzman rats. The effect was dose dependent over the range 10(-2)-10(-6) M, with a peak at 10(-3) M. Of more than 30 compounds tested by this protocol only known carcinogens and UV irradiation have been shown to produce more DNA damage than MH. MH treatment of hepatocytes for 30, 90, and 180 min clearly decreased the sedimentation velocity of hepatocellular DNA on alkaline sucrose gradients, indicating the formation of alkaline-labile lesions. The present evidence, when considered in light of recent studies demonstrating the tumor-inducing ability of MH in rats lead to the conclusion the MH is a complete carcinogen. (10 Refs)

20. THE COMBINED ACTION OF X-IRRADIATION, DRUG AND HYPERTHERMIA ON THE DNA IN MAMMALIAN CELLS IN VITRO.

Djordjevic O, Kostic L
Radiological Lab., Inst. Nuclear Sciences 'Boris Kidric', POB 522, 11000 Beograd, Yugoslavia
Strahlentherapie; 157(1):46-49 1981

The effects of the alkylating cytostatic drug PTC on the production of radiation-induced single-strand breaks in DNA, and on the repair in L cells incubated at 37 C or 42 C were studied. The same amount of SSB is obtained when the cells are treated simultaneously with PTC and hyperthermia as when irradiated with 2,500 rad, but different rate in the rejoining was observed. There is no potentiation of SSB formation by pretreatment of cells with 10 ug PTC/ml for 2 hours at 42 C before irradiation, but in these cells less effective repair occurs. The effect of PTC on the rejoining of SSB induced with 2,500 rad depends on the drug's concentration and post-incubation time. (Author abstract) (11 Refs)

21. FORMATION AND REMOVAL OF 7,12-DIMETHYLBENZ[A]ANTHRACENE-NUCLEIC ACID ADDUCTS IN RAT MAMMARY EPITHELIAL CELLS WITH DIFFERENT SUSCEPTIBILITY TO CARCINOGENESIS.

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Carcinogenesis; 2(12):1327-1333 1981

The susceptibility of the rat mammary gland to 7,12-dimethylbenz[a]anthracene (DMBA)-induced carcinogenesis is max when DMBA is fed to young virgin rats, diminishing with increasing age and becoming almost nil when pregnancy and lactation occur prior to carcinogen administration. This present study was carried out to determine whether these differences in susceptibility to DMBA are related to the ability of the gland to form and/or remove DMBA-nucleic acid adducts. Primary mammary epithelial cell cultures derived from young virgin (YV), old virgin (OV) and parous (P) Sprague-Dawley rats were treated in vitro with [3H]-DMBA for 24 hr. Hydrolysates of DNA isolated from these cells were chromatographed on Sephadex LH-20 columns. In cells from the three groups of animals, the chromatographic profiles were qualitatively similar with three 3H-labeled products eluting in the region expected for hydrocarbon-nucleoside adducts. This similarity in profiles suggested that identical DMBA-nucleic acid adducts are generated in each group. The chromatographic data are also consistent with the hypothesis that the hydrocarbon-DNA adducts of DMBA were generated through reactions of a 'bay-region' diol-epoxide of DMBA with DNA. Excision of DMBA-DNA adducts was investigated by measuring the time-dependent decrease in specific activity of the less dense parental DNA peak following centrifugation on alkaline CsCl gradients. Within 48 hr post-DMBA treatment, P cells removed approx 36% of the adducts from DNA with YV and OV cells removed only 24% and 12% of the adducts respectively. In addition, P cells excised the adducts at a rate 1.5 and 5x faster than either YV or OV cells. These results suggest that the lower susceptibility of the parous rat towards DMBA-induced carcinogenesis may be due not to the generation of different DMBA-DNA adducts, but to a more efficient DNA repair mechanism that is the result of increased gland differentiation through the process of pregnancy and lactation. (Author abstract) (56 Refs)

22. ISOLATION AND PARTIAL CHARACTERIZATION OF MUTAGEN-SENSITIVE AND DNA REPAIR MUTANTS OF CHINESE HAMSTER FIBROBLASTS.

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(c/o Trosko) Dept. Pediatrics and Human Development, Coll. Human Medicine, Michigan State Univ., East Lansing, MI, 48824
Environ Mutagen; 3(1):53-64 1981

Isolation and partial characterization of several mutants of Chinese hamster cells, which are affected in their ability to repair DNA damage or in their sensitivity to radiation or chemical mutations, are discussed. Cells of a subclone of the V79 aneuploid cell line were mutagenized by combined treatment with 5-bromodeoxyuridine and blacklight, followed by UV irradiation. 3H-thymidine was incorporated in repair-proficient cells at high temperature (38.5 C) following UV damage. Cells were held in the cold (4.0 C) to induce radioactive thymidine killing. Repair-deficient and UV-sensitive cells which had survived and formed colonies at low temperature (34.0 C) were tested for recovery. Seventy-two surviving colonies were isolated from 2 x 10(7) cells plated for selection. Four colonies were selected for extensive study. Colony UVs-7 was slightly more sensitive to UV, but not sensitive to x-rays or N-acetoxy-2-acetylaminofluorene (NAc-AAF); this mutant exhibited a highly reduced level of unscheduled DNA synthesis (UDS), as compare to the parental line. UVs-40 and UVs-44 line colonies were sensitive to UV, x-ray, N-methyl-N-nitro-N-nitrosoguanidine, and NAc-AAF, but exhibited normal UDS. Line UVr-23 had enhanced UDS, was resistant to UV, but exhibited no difference in sensitivity to x-ray or NAc-AAF. These four mutants are all stable, and may be useful for the study of mammalian DNA repair processes and mechanisms of mutagenesis. (38 Refs)

23. RELATIONSHIP BETWEEN EXCISION REPAIR AND UV TOLERANCE IN MOUSE CELLS (MEETING ABSTRACT).

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Division of Genetics, National Institute of Radiological Science, Chiba, Japan
Proceedings of the Japanese Cancer Association 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Excision repair plays an essential role in radiation carcinogenesis as evidence in human disorder xeroderma pigmentosum (XP). There is a correlation between UV resistance and excision repair in XP cells. This is not the case in mouse cells that are low in dimer excision but are as resistant to UV killing as are normal human cells. We have isolated a UV-sensitive mutant from mouse cells. The dimer removal was present to some extent in parental cells but absent in mutant cells. Postreplication repair was also examined. (no Refs)

24. CYTOTOXICITY, MUTAGENICITY AND DNA DAMAGE BY HOECHST 33342.

Durand RE, Olive PL
Section of Radiobiology, Johns Hopkins Oncology Center, Baltimore, MD, 21205
J Histochem Cytochem; 30(2):111-116 1982

Hoechst 33342 can be used for flow microfluorimetry (FMF) analysis of the DNA content of living Chinese hamster cells, giving good resolution (coefficients of variation (CVs) approx 6%) with relatively nontoxic staining regimens. The dye is, however, a very efficient inhibitor of DNA synthesis, with a marked depression of the DNA synthetic rate for V79 cells observed at concentrations 10-fold less than those required for optimal FMF resolution. Nontoxic and minimally toxic Hoechst concentrations also resulted in demonstrable mutation, as assayed by 6-thioguanine resistance. Hoechst disappearance from cel ls returned to normal growth medium after staining suggests two components of binding, since about half of the total strain is rapidly removed, whereas the rest is apparently diluted only by cell division. Cells containing Hoechst 33342 die more rapidly than control cells when held at 4 C and are also more susceptible to inactivation by the ultraviolet laser beam if operated at approx greater than or equal to 100 mW power. Thus, Hoechst 33342 can provide information about the DNA content of living cells, but at the expense of minimal toxicity, moderate mutation, and significant cell cycle perturbations. (Author abstract) (12 Refs)

25. STARVATION OF ARGININE AND GLUTAMINE SENSITIZES HUMAN DIPLOID CELLS TO THE TRANSFORMING EFFECTS OF N-ACETOXY-2-ACETYL-AMINOFLUORENE.

Zimmerman RJ, Little JB
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Carcinogenesis; 2(12):1303-1310 1981

We have examined the influence of the method of synchronization on the transformation of normal human diploid fibroblasts treated in mid-S phase with N-acetylaminofluorene (N-Ac-AAF), and on the subsequent kinetics of the removal of carcinogen damage. At early times posttreatment, the transformation frequency in cultures synchronized by a 24 hr starvation for arginine and glutamine was enhanced over that of cultures synchronized by release from confluence. In cells synchronized by either method, transformation was enhanced at all times when the cells were incubated after treatment in medium containing high concentrations of nonessential amino acids, vitamins and serum. Synchronized cells treated with 3 uM [3H]N-Ac-AAF in mid-S removed significantly less DNA damage than cultures treated and held under confluent, noncycling conditions. Cells synchronized by amino acid starvation removed less damage than cells synchronized by release from confluence. S-phase treatment of synchronized cells resulted in a dose-dependent delay of DNA replication. The early, rapid phase of repair was temporally correlated with the delay in S-phase progression. We conclude from these data that synchrony achieved by amino acid starvation renders human cells more sensitive to N-Ac-AAF-induced transformation in vitro than does that achieved by release from density-inhibition of growth. The S-phase treated, cycling cells lost only about 10% of their initial carcinogen damage before reinitiation of treatment-delayed bulk DNA synthesis. These results support the hypothesis that the persistence of carcinogen damage in replicating DNA may be an important factor in cell transformation. (Author abstract) (46 Refs)

26. UNSCHEDULED DNA REPAIR IN THE HUMAN CORNEA FOLLOWING SOLAR SIMULATING RADIATION.

Grabner G, Brenner W
Dept. Opthalmology II, Univ. Vienna, Alserstrasse 4, A 1090 Vienna, Austria
Acta Ophthalmol (Copenh); 59(6):847-853 1981

Human corneas were exposed in vitro to solar-simulating radiation (UVB), UVA radiation (controls), or no UV radiation (controls), and autoradiography with tritiated thymidine was performed to investigate the effect of UVB on corneas at the molecular level. Sparsely labelled nuclei, indicating unsched-

uled thymidine-dimer repair DNA-synthesis (dark repair), were observed in all cellular compartments of the UVB-irradiated corneas but not in the control specimens. Ratios of sparsely labelled cells/100 and grains/nucleus were low in the corneal epithelium and significantly higher in the stromal cells and endothelium. The fragile monolayer of endothelial cells thus consequently need protective mechanisms to overcome permanent radiation damage. Findings of high enzymatic dark repair activity seem to indicate excellent healing reserves of the endothelial cells. (14 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN INVERTEBRATES AND LOWER EUKARYOTES

27. REPAIR OF MITOCHONDRIAL DNA IN SACCHAROMYCES CEREVISIAE. INDUCTION OF CYTOPLASMIC PETITE MUTANTS IN A NUCLEAR MUTANT EXHIBITING THERMOSENSITIVE MITOCHONDRIAL DEOXYRIBONUCLEASE ACTIVITY.

Foury F
Laboratoire d'enzymologie, 1348, Louvain-la-Neuve, Belgium
J Biol Chem; 257(2):781-787 1982

Four nuclear thermosensitive mutants have been obtained in which induction of up to 100% cytoplasmic petite mutants (rho-) is observed upon cell incubation at 36 C. For a given incubation time at 36 C, the percentage of rho- is increased by preliminary gamma-ray irradiation. Under these conditions, the induction of rho- is a linear function of the irradiation dose. The retention of genetic information by rho- and of mitochondrial DNA synthesis in vivo and in vitro exclude that the mutants are deficient in the replication of mitochondrial DNA. The degradation of mitochondrial DNA labeled with [3H]dTTP in isolated mitochondria, has been monitored at 26 C and at 36 C after addition of 0.5% Triton X-100 in the presence or in the absence of ethidium bromide. In assays carried out at 26 C, the degradation of mitochondrial DNA is similar in the parental strain and in the mutant gamma s rho 2. However, at 36 C, the degradation of mitochondrial DNA is slower in the mutant. We have shown that a mitochondrial membrane deoxyribonuclease acting on double-stranded DNA at acid pH is thermosensitive in the mutant. Analysis of the meiotic segregants of a tetrad issued from the cross of the mutant with an isogenic parental strain shows co-segregation of rho- induction and of nuclease thermosensitivity in a 2:2 Mendelian pattern. These results suggest that a mitochondrial deoxyribonuclease is involved in the repair of damages caused to mitochondrial DNA by elevated temperature and by gamma-rays. (Author abstract) (29 Refs)

28. MITOCHONDRIAL TOXICITY IN SACCHAROMYCES AS A MEASURE OF CARCINOGENICITY.

Patel R, Wilkie D
Dept. Botany and Microbiology, Univ. Coll., London, England
Mutat Res; 100(1-4):179-183 1982

Primary antimitochondrial activities of 4-chloromethylbiphenyl (4CMB), benzyl chloride, and 4-hydroxymethylbiphenyl (4HMB) were identified by selective inhibition of cell growth in non-fermentable medium, induction of the mitochondrial mutation petite, and selective blockage of mitochondrial protein synthesis. Only the biphenyls appeared to be carcinogenic based on their antimitochondrial activity; neither can be considered a potent carcinogen and 4CMB appears weaker than 4HMB. (2 Refs)

MACROMOLECULAR BINDING OF CARCINOGENS

29. INTERACTION OF AFLATOXIN B2 WITH RAT LIVER DNA AND HISTONES IN VIVO.

Groopman JD, Fowler KW, Busby WF, Wogan GN
Boston Univ. Sch. Public Health, 80E Concord St., Boston, MA, 02118
Carcinogenesis; 2(12):1371-1373 1981

The interaction of aflatoxin B2 (AFB2) in vivo with rat liver nuclear macromolecules was examined in an attempt to correlate this binding with biological potency. The incorporation of [3H]AFB2 residues into rat liver histones and DNA was determined 2, 24 and 48 hr following administration of a single ip dose of 1 mg [3H]AFB2/kg body weight. At each time point, histone H1 and the total histone fraction contained 5-30-fold more [3H]AFB2 moieties than did DNA on a weight basis. Analytical reversed-phase hplc of the acid hydrolysis products resulting from AFB2 binding to DNA revealed that 85% of the radioactivity cochromatographed with the major aflatoxin B1-DNA adduct, 2,3-dihydro-2-(N7-guanyl)-3-hydroxyaflatoxin B1. These studies revealed an apparent correlation between AFB2 derived binding to DNA in vivo in rats and its potency as a toxin and carcinogen in this species. (Author abstract) (14 Refs)

30. RNA BREAKAGE ACTIVITY OF THE METHANOL EXTRACT OF AUROMOMYCIN.

Kalvin DM, Huang CH, Lischwe MA, Peters EH, Prestayko AW, Crooke ST
816 Tappan, apt. 10, Ann Arbor, MI, 48104
Cancer Chemother Pharmacol; 7(1):41-50 1981

Components of the antitumor antibiotic auromomycin (AM) were characterized. An AM preparation (AM0) was extracted using methanol. Absorption studies indicated that the extract (AMX) contained 70% of the non-peptide chromophore contained in AM0; the residue (AMR) contained 20% of the chromophore. AMX contained 21-26% of the peptides in AM0. AMX exhibited 121% +-28% of the capacity (DDC) of AM0 to degrade PM-2 DNA. AMR exhibited 22% +-3.8% of the DDC of AM0. A mixture of AMX and AMR had a DDC 78% +-6.7% less than that of AM0. AMX showed a DDC against single-stranded DNA 6.5x that against double-stranded DNA, as indicated by agarose gel electrophoresis. Differences in total DDC of AM0, AMX, AMR, and AMX + AMR were attributed to possible interactions between peptides and the non-peptide chromophore in the AM0 and the mixture of AMX and AMR. Fractionation of AMX by means of Sephadex chromatography produced several fractions showing DDC that contained enriched non-peptide chromophore relative to peptides. Exposure of AMX to UV radiation eliminated DDC. Results indicate that DDC of AM is due to the non-peptide chromophore component. (24 Refs)

31. COMPARATIVE STUDIES ON THE PHOTOSENSITIZING POTENCY OF 5-METHOXYPSORALEN AND 8-METHOXYPSORALEN AS MEASURED BY CYTOLYSIS IN PARAMECIUM CAUDATUM AND TETRAHYMENA PYRIFORMIS, AND GROWTH INHIBITION AND SURVIVAL IN CANDIDA ALBICANS.

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Photochem Photobiol; 35(1):83-88 1982

The photosensitizing potencies of 5-methoxypsoralen and 8-methoxypsoralen were investigated using the following biological end-points for lethality: (i) cytolysis in the protozoans Paramecium caudatum and Tetrahymena pyriformis, (ii) inhibition of growth in the yeast Candida albicans and (iii) survival as measured by colony counts in Candida albicans. In all cases, 5-methoxypsoralen proved to be the more potent photosensitizing agent. The preliminary action spectra of the two compounds for growth inhibition in C albicans were similar and showed maximal spectral efficiency in the 320-340 nm waveband. The molecular basis for the described end-points is unknown. Although it is well known that 5-methoxypsoralen and 8-methoxypsoralen readily photoreact with DNA, it is considered that photoreaction with protein should also be given serious consideration as the possible lethal event. The superior effect of 5-methoxypsoralen is in accordance with some of the physical and photochemical properties of this molecule, but this result is at variance with other studies in different test systems that have been used to compared the photobiological efficacy of these two compounds. (Author abstract) (37 Refs)

32. PRIMARY MECHANISMS OF PHOTOSENSITIZATION BY FUROCOUMARINS.

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Dept Physics, Illinois Inst. Tech., Chicago, IL

Proceedings of the International Symposium on Psoriasis, held in Stanford, California, July 13, 1981. Available from National Technical Information Service, Springfield, VA, as DOE/EV/02217-39:, 11 pp., 1981.

A proper understanding of the PUVA therapy action mechanism requires the synthesis of concepts developed at the level of molecules, single cells and whole organisms. Although progress has been made in identitying key factors within each level of organization, the interrelationships remain obscure. Important unanswered questions at the molecular and cellular levels include: (1) which excited states of the furocoumarin in molecule (triplet or excited singlet) are involved in the formation of DNA monoa dducts, and the conversion of monoadducts to cross-links. (2) How does the spectrum of the incidence radiation affect the distribution of the initial photochemical products from the PUVA sensitizers. (3) What are the relative contributions of furocoumarin-DMA monoadducts, furocoumarin-DNA cross-links and singlet oxygen to mutagenesis and lethality in cells, at the furocoumarin and UV-A dose levels corresponding to PUVA therapy. Additional information about these key aspects of furocoumarin photosensitization should lead to a more definitive relationship of the cellular level events to the endpoints observed with PUVA therapy, and suggest directions for potential improvements in the current clinical procedures. (Author abstract)

33. MONOFUNCTIONAL COVALENT PHOTOBINDING OF DICTAMNINE, A FUROQUINOLINE ALKALOID, TO DNA AS TARGET IN VITRO.

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Photochem Photobiol; 35(1):63-68 1982

The naturally occurring furoquinoline alkaloid, dictamnine, is phototoxic to Gram-positive bacteria, yeasts and filamentous fungi in the presence of long-wave UV light. Prior to photobinding to DNA dictamnine forms a complex with the macromolecule in the dark. Photobinding to DNA is shown with [3H]-dictamnine. In contradiction to an earlier finding, dictamnine proved to be incapable of forming interstrand crosslinkages with native DNA. This fact was ascertained by the use of methods additional to hydroxyapatite column chromatography, eg alkaline sucrose gradient centrifugation and hyperchromicity tests. The alkaloid therefore represents a new monofunctional photoreagent towards DNA in vitro. It is assumed that it binds through its furyl-C=C to DNA. The inability to form crosslinks may be attributed to the stability of the lateral aromatic nucleus. As no photoreactivity against human erythrocytes could be observed, it is possible that nucleic acids represent the major target of damage in vivo. (Author abstract) (49 Refs)

34. LIGHT-ENHANCED GENETIC TOXICITY OF OF CRYSTAL VIOLET.

Levin DE, Lovely TJ, Klekowski E
Biochemistry Dept., Univ. California, Berkeley, CA, 94720

Mutat Res; 103(3-6):283-288 1982

The light-enhanced genetic toxicity of crystal violet (CV) and the effect of Aroclor 1254-induced rat-liver S9 fraction on its genetic toxicity in the Rosenkranz (Escherichia coli polymerase A-) assay and the Ames (Salmonella TA98, TA100, and TA1537) test were studied. The Rosenkranz assay showed a dark-incubation genotoxic effect of CV, which was enhanced under light incubation. The presence of S9 had no effect on the genetic toxicity of CV in the Rosenkranz assay. In the Ames assay CV exhibited no mutagenic activity in any strain; CV at 5.0 ug/plate sterilized the plates under dark incubation, and this effect was enhanced under light incubation. S9 whether enzymatically active, thermally inactivated, or not buffered, eliminated the toxicity of CV for the strains of Salmonella. The nutritive value of S9 or a possible binding of CV to S9 proteins, are suggested as possible explanations for the protective activity of S9 when its enzymatic activity is destroyed. (12 Refs)

35. RELATIONSHIPS BETWEEN MICROSOMAL METABOLISM, DNA DAMAGE AND ADDUCT BINDING IN POLYCYCLIC HYDROCARBON-EXPOSED LUNG (MEETING ABSTRACT).

Haski R, Stewart BW
Department of Pathology, University of New South Wales, Kensington, Australia

Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

Preparations of isolated lung DNA from rats treated by intra-tracheal instillation of 3-methylcholanthrene (3MC) may be distinguished from control preparations by the extent of structural damage to the nucleic acid. In the study to be described, damage to DNA was determined by benzoylated-diethylaminoethyl cellulose chromatography. To analyze the

relationship between metabolism of 3MC and subsequent DNA damage, the effect of modifiers of cytochrome P-450 (P-450) on both parameters was examined. Initially, measurement was made of P-450 content of rat lung at various times after administration of the hydrocarbon. In this manner experimental conditions for the use of an inducing dose of 3MC were determined and criteria were available to examine the efficacy of carbon tetrachloride-inhalation as a means of inhibiting 3MC metabolism. Animals were then treated either with an inducing dose of 3MC or by prior exposure to carbon tetrachloride to perturb microsomal metabolism of the carcinogen. The subsequent effect, on 3MC-induced DNA damage and repair, was determined. In addition, the co-valent binding of 3MC to lung DNA was assayed using LH-20 chromatography. The findings indicate that the extent of polycyclic hydrocarbon-induced DNA damage in lung may be subject to wide variation as a consequence of exposure to agents which modifiy the rate of carcinogen metabolism. (no Refs)

36. RADIATION-INDUCED STRUCTURAL CHANGES IN HUMAN ERYTHROCYTE MEMBRANE PROTEINS REVEALED BY SODIUM DODECYL SULFATE/ POLYACRYLAMIDE GEL ELECTROPHORESIS.

Todo T, Yonei S, Kato M
Lab. Radiation Biology, Faculty of Science, Kyoto Univ., Kitashirakawa, Sakyo, Kyoto 606, Japan
Radiat Res; 89(2):408-419 1982

Differences in the radiosensitivity of the major proteins of human erythrocyte membranes was investigated. It was determined that disulfide formation is a minor event and more complex reactions are involved in the radiation-induced damage to membrane proteins. Analysis of the proteins by sodium dodecyl sulfate/polyacrylamide gel electrophoresis revealed the appearance of both cross -linked aggregates and radiolytic products of spectrin. Spectrin was the most sensitive of the erythrocyte membrane proteins to x-irradiation. (34 Refs)

37. CHARACTERIZATION OF RIBONUCLEASE A IRRADIATED WITH GAMMA-RAYS IN THE PRESENCE OF CYTIDYLIC ACID WITH RESPECT TO THE INTERACTION OF THE ENZYME WITH FOLIC ACID.

Sawada F, Irie M
Div. Chemistry, National Inst. Radiological Sciences, Anagawa, Chiba 260, Japan
J Radiat Res (Tokyo); 22(3):367-372 1981

The folic acid-binding site on bovine pancreatic ribonuclease A (RNase A) and its modification by gamma-irradiation in the presence of cytidine 2'(3')-phosphate (CMP) were studied. Gamma-irradiation of RNase A in the presence of CMP produced enzymatically active derivatives of the enzyme. Results suggest that not only the main active site (B1-R1-p1) but also the sub-site (B2) remains intact after gamma-irradiation under the conditions used. (11 Refs)

EFFECT OF CARCINOGENS ON MACROMOLECULAR SYNTHESES

38. X-RAY INHIBITION OF DNA SYNTHESIS AT DISCRETE TIMES DURING S PHASE IN SYNCHRONOUS HUMAN DIPLOID FIBROBLASTS.

Kapp LN, Painter RB
Lab. Radiobiology, Univ. California, San Francisco, CA, 94143
Radiat Res; 89(2):424-427 1982

The incorporation of thymidine into irradiated and unirradiated diploid fibroblasts at various times during S phase was investigated. Results indicated that most replicons initiate during relatively restricted times in S phase. Results support a model of diploid fibroblast S phase that consists of multiple initiations of large numbers of replicons during short, specific times. (12 Refs)

39. ACTION OF X-RAYS AND NEURAMINIDASE ON PINOCYTOTIC ACTIVITY AND MICROTUBULE-MICROFILAMENT SYSTEM OF EHRLICH ASCITES TUMOR CELLS IN MONOLAYER CULTURE.

Pfab R, Schachtschabel DO, Paul N, Kern HF, Hess F
Klinik und Poliklinik fur Strahlentherapie und Rontgendiagnostik, Univ. Marburg, Robert-Koch-Str. 8a, D-3550 Marburg, W. Germany
Strahlentherapie; 157(7):468-473 1981

Monolayer cultures of Ehrlich ascites tumor cells in exponential growth phase were treated with x-rays and neuraminidase alone or in combination. A radiation dose of 2 Gy (200 rad) and higher effected a significant inhibition of DNA synthesis and cell proliferation. Neuraminidase treatment in addition to irradiation did not modify the growth-inhibitory irradiation effect. Cells pretreated for 0.5 to 1.0 hr with neuraminidase (in Earle's salt solution) and cultured thereafter (4 hr) in serum-containing growth medium exhibited an enhanced development of the microtubule-microfilament-system. Morphometric analysis of microtubules on electron-microscopic sections revealed a nearly four-fold increased number in neuraminidase treated cells while the average length of microtubules was similar to controls. Pinocytosis as measured by the ultrastructural uptake of ferritin appeared to be increased following neuraminidase treatment. A connection between neuraminic acid containing components (glycoproteins or glycolipids?) of the cell membrane or cell surface, on the one hand, and the cytoskeleton and the endocytotic process of these tumor cells, on the other hand, is suggested. (Author abstract) (25 Refs) (In GER)

40. A STUDY ON THE LOST NUCLEAR RNA IN AZODYE-INDUCED HEPATOMA (MEETING ABSTRACT).

Akao M, Kuroda K
Department of Toxicology and Experimental Pathology, Research Institute Chemobiodynamics, Chiba University, Chiba, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

DNA-RNA competitive hybridization study with the use of terminally 32P-labeled nuclear RNA (nRNA) indicated definitely the loss of some nRNA species in 3'-Me-dimethylaminoazobenzene (DAB) induced hepatoma. No such deletion was found in the livers of rats fed 3'-Me-DAB, alone or in combination with phenobarbital. The nRNA species that were present in liver and lost in hepatoma were then fractionated. The pertinent RNAs were found to exist among those whose sedimentation coefficients were less than 14S under su-

crose density gradient centrifugation, and polyacrylamide gel electrophoresis indicated that these RNAs were fast-moving low mol wt ones. (no Refs)

41. RADIOAUTOGRAPHIC STUDIES ON INCREASE AND DECREASE OF MITOCHONDRIA AND PEROXISOMES AND THEIR NUCLEIC ACID SYNTHESIS IN RAT HEPATIC CELLS BEFORE AND AFTER DEHP ADMINISTRATION (MEETING ABSTRACT).

Nagata T, Fujii Y
Department of Anatomy, Shinshu University School of Medicine, Matsumoto, Japan
Proceedings of the Japanese Cancer Association 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Hepatic cells of rats treated with di-2-ethylhexylphthalate (DEHP) were studied by means of light and electron microscopic radioautography. Fifty Wistar rats were fed a diet containing 1, 2 and 4% DEHP for 1 to 42 days, while 16 rats fed the diet for 14 days then fed with normal diet for 1 to 42 days. The liver tissues were incubated in vitro in two kinds of media consisting of Eagle's minimum essential medium containing either 3H-thymidine or 3H-uridine, fixed, embedded in Epon, sectioned and radioautographed. The number of vol of mitochondria and peroxisomes and the silver grains over them increased during DEHP administration, and decreased after its withdrawal. It is concluded that these organelles increased after administration of DEHP synthesizing both DNA and RNA, then decreased after its withdrawal decreasing the rate of nucleic acid synthesis. (no Refs)

42. THE TIME NEEDED FOR NORMALIZATION OF HAIRLESS MOUSE EPIDERMIS AFTER TREATMENT WI TH TWICE WEEKLY TOPICAL SKIN APPLICATIONS OF 10 NMOL 12-O-TETRADECANOYLPHORBOL-13-ACETATE IN ACETONE, OR ACETONE ALONE, FOR 18 WEEKS. A MORPHOLOGIC AND CELL KINETIC STUDY.

Iversen OH, Paulsen JE, Schjolberg A
Inst. Pathology, Univ. Oslo, Rikshospitalet, Oslo 1, Norway
Carcinogenesis; 2(12):1353-1358 1981

In order to find the time needed for normalization of the mouse epidermis after an 18 wk-course of treatment according to the two-stage carcinogenesis protocol, hairless mice were treated with 10 nmol 12-O-tetradecanoylphorbol-13-acetate in 100 ul reagent grade acetone twice weekly for 18 wk. A control group was treated similarly with 100 ul reagent grade acetone alone. Groups of four animals were killed each wk for 10 wk thereafter, and morphologic and cell kinetic studies performed. To assess hyperplasia, the number of basal and suprabasal cells per unit length of epidermis was counted. The mitotic rate was determined by a stathmokinetic method using Colcemid for arrest of mitoses. DNA synthesis was measured by determining the labeling index and the DNA-specific activity after injection of [3H]thymidine. Flow cytometric measurements were performed to find the fraction of cells in the various cell cycle phases at each observation point. Treatment with acetone alone led to a moderate hyperplasia and a slight increase in the mitotic rate, which persisted during the 10 wk of subsequent observation. Treatment with TPA led to a considerable hyperplasia which first increased for 3 wk and then decreased, and was still significant 10 wk after termination of treatment. The line of best fit through the values indicated that a time of about 20 wk may be needed before normal epidermal thickness is reestablished. TPA treatment also led to a pronounced increase in the labeling index and a high mitotic rate. These variables became almost normal after approx 8-10 wk, but one cannot know whether one or more new waves of proliferation take place more than 10 wk after termination of TPA treatment. If a proper 'inverse' experiment according to the two-stage theory of carcinogenesis should be performed, one had to wait at least 20 wk after termination of promotion before the initiating dose of carcinogen should be applied. The possibility of increased acquired resistance to carcinogens during promotion is also discussed. (Author abstract) (10 Refs)

REVIEWS

43. ALKYLATION OF DNA AND TISSUE SPECIFICITY IN NITROSAMINE CARCINOGENESIS.

Montesano R
International Agency for Res. on Cancer, 150, Cours Albert Thomas, 69372 Lyon Cedex 2, France
J Supramol Struct Cell Biochem; 17(3):259-273 1981

Evidence that the initintion of the carcinogenic process by nitrosamines is linked to the metabolic competence of the target tissue or cell to convert carcinogens into mutagenic metabolites, and to the binding of those metabolites to cellular DNA is reviewed. Alkylation of DNA occurs at the N-1, N-3, and N-7 positions of adenine; N-3, N-7, and O6 of guanine; N-3 and O2 of cytosine; N-3, O4, and O2 of thymine; and the phosphate groups. The initial proportion of each DNA adduct depends upon the alkylating agent. Alkylation at the oxygen atoms of DNA bases is more critical than alkylation at other positions in the mutagenesis and carcinogenesis induced by N-nitroso compounds. Tissues in which tumors occur more frequently are those in which O6-alkylguanine persists longest in DNA. The more rapid removal of O6-methylguanine from DNA of rat liver is associated with the absence of tumor production in this organ by a single dose of dimethylnitrosamine (DMN). Significant incidence of liver tumors is observed if the same dose is given 24 hr after partial hepatectomy. Data indicate that the rate of disappearance of 7-methylguanine from the liver or extrahepatic tissues is independent of DMN dose; O6-methylguanine is lost from DNA more rapidly after a low dose of DMN. The removal of O6-methylguanine from DNA can be affected by pretreating the animals with N-nitroso compounds. The modulation of DNA repair processes is discussed in relation to the tissue-specific carcinogenic effect of N-nitroso compounds. (132 Refs)

44. ANTIBODIES SPECIFIC FOR DNA COMPONENTS STRUCTURALLY MODIFIED BY CHEMICAL CARCINOGENS.

Muller R, Rajewsky MF
(c/o Rajewsky) Institut fur Zellbiologie (Tumorforschung), Universitat Essen (GH), Hufelandstrasse 55, Essen 1, W. Germany
J Cancer Res Clin Oncol; 102(2):99-113 1981

Preparation, properties, and applications of antibodies against carcinogen-DNA adducts are reviewed. Specific topics discussed are procedures for the coupling of carcinogen-modified nucleosides (haptens) to carrier proteins, immunization procedures and carrier proteins used for antibody production, assays of antibody specificity and affinity, quantitative immunologic assays of carcinogen-modified DNA components, and use of the antibodies in in vivo and cell culture experiments. (69 Refs)

45. AN EVALUATION OF TESTS USING DNA REPAIR-DEFICIENT BACTERIA FOR PREDICTING GENOTOXICITY AND CARCINOGENICITY. A REPORT OF THE U. S. EPA'S GENE-TOX PROGRAM.

Leifer Z, Kada T, Mandel M, Zeiger E, Stafford R, Rosenkranz HS
Dept. Microbiology, New York Medical Coll., Valhalla, NY, 10595
Mutat Res; 87(3):211-297 1981

Methods for detection of DNA-damaging agents by repair-deficient bacterial assays are reviewed and recommendations for their improved use are made. Literature through April 1979 was searched and 91/276 papers contained analyses of 611 compounds that had been assayed in one or more of 55 pairs of repair-proficient and repair-deficient strains (38 Escherichia coli, 11 Bacillus subtilis, and 6 Prote us mirabilis). Test results and carcinogenicity data were compared in polA and other E coli, and E coli polA and B subtilis systems. In the E coli polA system, 100/269 compounds tested were positive, 35 negative and 134 gave No Test (NT) by the spot method; 24 of the latter compounds tested were also positive in the liquid assay technique. Among 45 compounds with a NT result, 23 were positive in the liquid assay and 22 were negative. When the E coli polA system was compared with other E coli strains, agreement of results was observed for 10 compounds, while 7 that were positive with polA and some of the other E coli strains were negative with WP2uvrA. A 78% correspondence between E coli polA and B subtilis rec assays was observed. Of 71 carcinogens assayed by the polA system, 44 were positive, 10 negative, and 17 gave NT or doubtful results. Of 56 carcinogens assayed with B subtilis, 21 were positive, 9 negative and 26 were NT or doubtful. One noncarcinogen tested in each assay was positive. Of the seven carcinogens assayed in P mirabilis, six were positive. E coli detected the highest percentage of alkyl epoxides and hydroxylamines; B subtilis rec the highest percentage of nitrosamines and sulfur and nitrogen oxides. Advantages and disadvantages of DNA repair assays in bacteria are listed. (98 Refs)

46. POLYAMINES IN MAMMALIAN TUMORS PART 1.

Scalabrino G, Ferioli ME
Inst. General Pathology, Univ. Milan, 20133 Milan, Italy
Adv Cancer Res; 35:151-268 1981

The connection between polyamines (PA) and cancer in mammals is reviewed, and evidence of a relationship between PA and neoplastic disease is evaluated. Biochemical and metabolic aspects discussed include properties of the PA biosynthetic enzymes S-adenosyl-L-methionine, 5'-methylthioadenosine, catabolism of major PA in mammals, conjugation and excretion products, and natural antibodies of PA. Levels of PA and biosynthetic enzymes in experimental tumors and modifications of in vivo and in vitro metabolism of PA by chemical carcinogens and tumor promoters (single and repeated promoter administration, multistage carcinogenesis, mutagenic and antimutagenic properties of PA) are reviewed. PA levels in urine, serum, and erythrocytes of rats during chemical carcinogenesis or when bearing several experimental tumors are considered. Effects of oncogenic RNA and DNA viruses in biosynthesis, levels of PA in cells during virus-induced transformation, and the role of physical carcinogens in changes in PA biosynthesis and content of target tissues are reviewed. (894 Refs)

47. CHEMICAL CARCINOGENESIS AND SMOKING.

Farber E
Dept. Pathology, Univ. Toronto, Banting Inst., 100 College St., Toronto, Ontario M5G 1L5, Canada
Can J Public Health; 72(6):381-385 1981

Development of cancer in the respiratory tract in relation to some of the steps for carcinogenesis is reviewed. Metabolic activation of the majority of the known carcinogens is a prerequisite for interactions with DNA and other cellular components. Genetic defects in repair processes in cells may lead to increase in sensitivity to some carcinogenic influences, and the role of cell proliferation is important. The next step in carcinogenesis is promotion, the selective stimulation of initiated cells to grow. Suggested mechanisms of promotion are differential inhibition, stimulation, necrosis with regeneration, and recovery. Regression or maturation to normal-appearing tissue appears to be entirely dependent on the environment. Persistence of focal proliferations with a greatly increased risk for development of a second focal change is considered to be the first neoplastic step. Important component of cancer development with smoking is the promoting effect of components in the smoke. Later precancerous changes characterized by cytologic and histologic alterations show biological reversibility. Studies indicated a presence of a distinctive enzyme and other markers very early in carcinogenesis and long before any cytologic evidence of alteration appears. In the bladder, the early cells in man and in animal show chages in staining for alkaline phosphatase. The observations point to possibility of developing characteristic staining procedures that should enable the identification of early preneoplastic or premalignant changes in bronchial epithelial cells. (30 Refs)

48. RETINOID BINDING IN NORMAL AND NEOPLASTIC MAMMARY TISSUE.

Moon RC, Mehta RG
Life Sciences Div., IIT Res. Inst., 10 West 35th St., Chicago, IL, 60616
Adv Exp Med Biol; 138:231-249 1982

Characterization of cytosolic retinoid binding proteins and nuclear translocation of cytosolic retinoic acid binding protein (cRABP) in mammary tissue during normal and neoplastic differentiation are reported. Relatively high levels of cRABP were observed in the mammary glands from pregnant animals as well as in ovarian hormone independent tumors; in glands obtained from lactating rats and in hormone dependent tumors, lower levels of cRABP were evident. Results indicate a possible correlation between endocrine and retinoid function in both normal and neoplastic differentiation of mammary tissue. A possible selective inhibition of ovarian hormone independent tumors by the retinoids is indicated. (52 Refs)

* U. S. GOVERNMENT PRINTING OFFICE : 1982—361-847/120

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. AN EVALUATION OF THE GENETIC TOXICITY OF EPICHLORHYDRIN. A REPORT OF AN EXPERT GROUP OF THE INTERNATIONAL COMMISSION FOR PROTECTION AGAINST ENVIRONMENTAL MUTAGENS AND CARCINOGENS.
Sram RJ, Tomatis L, Bridges BA, Clemmesen J
(c/o Lohman), Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(3):299-319 1981

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NIOSH Document Development Branch
Robert A. Taft Lab., National Inst. Occupational Safety and Health, 4676 Columbia Parkway, Cincinnati, OH, 45226
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RADIATION CARCINOGENESIS

4. CELLULAR TRANSFORMATION BY RADIATION: INDUCTION, PROMOTION, AND INHIBITION.
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J Supramol Struct Cell Biochem; 16(4):311-336 1981

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Hoffman DA, Felten RP, Cyr WH
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Nutr Cancer; 2(4):241-249 1981

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Dept. Biochemistry, Univ. Western Ontario, London, Ontario, N6A 5C1, Canada
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10. EPIDEMIOLOGY AND THE STUDY OF CANCER.
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13. HEALTH HAZARDS OF ASBESTOS EXPOSURE.
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Tola S
Dept. Epidemiology and Biometry, Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
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16. TRANSFORMATION INDUCED BY HERPES SIMPLEX VIRUS: A POTENTIALLY NOVEL TYPE OF VIRUS-CELL INTERACTION.
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(c/o Rajewsky) Institut fur Zellbiologie (Tumorforschung), Universitat Essen (GH), Hufelandstrasse 55, Essen 1, W. Germany
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Sangyo Igaku; 23(4):355-365 1981
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Inst. General Pathology, Univ. Milan, 20133 Milan, Italy
Adv Cancer Res; 35:151-268 1981

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SERIES CK11 No. 82/07

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BIOLOGICAL ASPECTS OF DNA ALTERATION AND REPAIR IN RELATION TO CARCINOGENICITY

1. TRANSFECTION OF CELLS FROM A XERODERMA PIGMENTOSUM PATIENT WITH NORMAL HUMAN DNA CONFERS UV RESISTANCE.

Takano T, Noda M, Tamura TA
Dept. Microbiology, Keio Univ. Sch. Medicine, Shinjuku-Ku, Tokyo-160, Japan
Nature; 296(5854):269-270 1982

Transfection of cells from a patient with xeroderma pigmentosum (XP) by DNA from normal human cells produced cells which were resistant to UV damage. XP20S skin fibroblasts from a XP patient were transformed by simian virus 40 (SV40) and established as a permanent cell line, XP20S(SV). The activity transforming the XP cells to UV resistance (UVr) was carried on the DNA molecules introduced into the transformed cells, because after treatment of donor A204 DNA with DNase I, there were very few UVr transformants. The sensitivity of the transforming activity of A204 DNA was tested with various restriction enzymes which recognize different hexanucleotide sequences at their cleavage sites. SalI and XhoI raised transformation efficiency whereas HindIII, BamHI and EcoRI removed the transforming activity. Many minute colonies were found in cultures treated with BamHI- and HindIII-digested DNAs; thes. digested DNAs appeared to slightly raise the UV-resistance of the recipient cell. UV-resistant XP20S(SV) cells transformed by both high-mol wt and restriction endonuclease-cleaved DNA from DNA donors A204 and MRC-5 showed stable UVr phenotypes during passage in culture; no revertants that were highly sensitive to UV were found. The resistant cells have presumably acquired a gene conferring UV resistance. (6 Refs)

2. DNA REPAIR IN NORMAL HUMAN AND XERODERMA PIGMENTOSUM GROUP A FIBROBLASTS FOLLOWING TREATMENT WITH VARIOUS METHANESULFONATES AND THE DEMONSTRATION OF A LONG-PATCH (U.V.-LIKE) REPAIR COMPONENT.

Snyder RD, Regan JD
Univ. Tennessee, Oak Ridge, TN, 37830
Carcinogenesis; 3(1):7-14 1982

Excision repair of DNA in normal and xeroderma pigmentosum complementation Group A fibroblasts was examined following treatment with methyl-methanesulfonate, ethyl-methanesulfonate and isopropyl methanesulfonate. Studies utilizing repair synthesis methods and inhibition with arabinofuranosyl cytosine revealed two distinct phases of repair; one commencing and terminating within the first 3-5 hr after the treatment, and a second, much longer phase extending from 9-35 hr post-treatment. Both phases of repair having a long-patch (uv-like) component, which establishes for the first time the existence of this mode of repair in response to alkane sulfonate damage. While xeroderma cells display somewhat fewer alkaline labile sites in their DNA following alkylation treatment than do their normal counterparts (consistent with earlier observations suggesting a deficiency in a glycosylase or apurinic endonuclease), we are unable to demonstrate a deficiency of these cells in either of the two phases of repair. (Author abstract) (61 Refs)

3. INDUCTION AND REPAIR OF PSORALEN CROSS-LINKS IN DNA OF NORMAL HUMAN AND XERODERMA PIGMENTOSUM FIBROBLASTS.

Bredberg A, Lambert B, Soderhall S
Dept. Clinical Genetics, Karolinska Hosp., S-104 01 Stockholm, Sweden
Mutat Res; 93(1):221-234 1982

Induction and repair of DNA damage produced by exposure to 8-methoxypsoralen (8-MOP) was studied in normal human fibroblasts and fibroblasts of the xeroderma pigmentosum (XP) line CRL 1223. Cells were labeled with [methyl-3H]thymidine. DNA damaged was assessed by alkaline elution. Cells were treated with UV-A irradiation, PUVA (8-MOP UV-A), PUVA UVA (PUVA UV-A alone 1 or 7 days after PUVA), or x-rays. Cells were exposed to 8-MOP (1 or 20 ug/ml) at 37 C for 1 hr. UV-A irradiation (0.04 or 1.1 Joules/square cm) was carried out at 0-4 C. UV-A treatment increased the elution rate of DNA; the increase returned to normal in cells incubated for 30 min after irradiation. Elution rates for cells treated with PUVA were not different from those for controls. Elution rates for cells treated with PUVA UVA were initially below control values; during post-treatment incubation elution rates increased above control levels for 7 days. Elution rates for XP cells did not change during post-treatment incubation. Results indicate that UV-A irradiation produces DNA breaks that are rapidly repaired during post-treatment incubation. PUVA treatment produces monoadducts of DNA that last for up to 7 days; subsequent UV-A treatment converts the monoadducts to DNA cross-links. Cross-links are repaired by a process involving formation of DNA breaks. XP cells do not repair DNA damage. (23 Refs)

4. INACTIVATION OF ULTRAVIOLET REPAIR IN NORMAL AND XERODERMA PIGMENTOSUM CELLS BY METHYL METHANESULFONATE.

Cleaver JE
Lab. Radiobiology and Environmental Health, Univ. California, San Francisco, San Francisco, CA, 94143
Cancer Res; 42(3):860-863 1982

Excision repair of ultraviolet damage in the DNA of normal and xeroderma pigmentosum (Groups C, D and variant) cells was inactivated by exposure of cells to methyl methanesulfonate immediately before irradiation independent of the presence of 0 to 10% fetal calf serum. The inactivation could be represented by a semilog relationship between the amount of repair and methyl methanesulfonate concentration up to approx 5 mM. The inactivation can be considered to occur as the result of alkylation of a large (about 10(6) daltons) repair enzyme complex, and the dose required to reduce repair to 37% for most cell types was between 4 and 7 mM. No consistent, large difference in sensitivity to methyl methanesulfonate was found in any xeroderma pigmentosum complementation group compared to normal cells, implying that reduced repair in these groups may be caused by small inherited changes in the amino acid composition (ie, point mutations or small deletions) rather than by losses of major components of the repair enzyme complex. (Author abstract) (19 Refs)

5. FAILURE OF RNA SYNTHESIS TO RECOVER AFTER ULTRAVIOLET IRRADIATION: AN EARLY DEFECT IN CELLS FROM INDIVIDUALS WITH COCKAYNE'S SYNDROME AND XERODERMA PIGMENTOSUM.

Mayne LV, Lehmann AR

(c/o Lehmann) MRC Cell Mutation Unit, Univ. Sussex, Falmer, Brighton, Sussex BN1 9QG, England

Cancer Res; 42(4):1473-1478 1982

Previous work has shown that in cells from the UV-sensitive genetic disorder, Cockayne's syndrome, DNA synthesis fails to recover after UV irradiation, despite the fact that these cells have no detectable defect in either excision or daughter-strand repair pathways. We now show that Cockayne cells, as well as cells from a number of patients with xeroderma pigmentosum, are sensitive to the lethal effects of UV irradiation in stationary phase under conditions in which no DNA is synthesized after irradiation. Furthermore, in normal and defective human fibroblasts, RNA synthesis is depressed after UV irradiation. In normal (dividing) cells, RNA synthesis recovers very rapidly, but this recovery does not occur in Cockayne cells, and it is reduced or absent in xeroderma pigmentosum cells from different complementation groups. Qualitatively, similar results are obtained with cells in stationary phase. The recovery of RNA synthesis in the various defective cell strains is not correlated with the overall extent of excision repair, but there is some correlation between recovery of RNA synthesis and cell survival after UV irradiation. These results implicate recovery of RNA synthesis as an important early response to UV irradiation. (Author abstract) (33 Refs)

6. A DEFICIENCY IN THE REPAIR OF UV AND GAMMA-RAY DAMAGED DNA IN FIBROBLASTS FROM COCKAYNE'S SYNDROME.

Rainbow AJ, Howes M

Dept. Radiology, McMaster Univ., Hamilton, Ontario L8S 4J9, Canada

Mutat Res; 93(1):235-247 1982

DNA-repair deficiencies were investigated in fibroblasts from five unrelated patients with Cockayne's syndrome (CS) and two patients heterozygous for CS. Suspensions of adenovirus type 2 were exposed to UV or gamma irradiation. Fibroblasts were then infected with irradiated or nonirradiated virus and then incubated. The fibroblasts were then assayed by immunofluorescence methods for expression of viral structural antigens. Results obtained from CS fibroblasts were compared with results obtained from normal and xeroderma pigmentosum (XP) fibroblasts. Host-cell reactivation (HCR) of viral function for both UV- and gamma-irradiated virus was reduced in homozygous CS fibroblasts. The dose of UV required to reduce viral function in homozygous CS fibroblasts by 37% (D37) was 14-35% of the D37 for normal cells. D37 for gamma-irradiation of CS cells was 61-80% of that for normal cells. One heterozygous CS strain had a D37 for UV-irradiated virus 68% of normal, intermediate between the D37 for homozygous CS and normal cells. The other heterozygous CS strain had a normal D37. Results indicate that CS fibroblasts have a defect in DNA repair mechanisms. (41 Refs)

7. LYMPHOBLASTOID LINES AND SKIN FIBROBLASTS FROM PATIENTS WITH TUBEROUS SCLEROSIS ARE ABNORMALLY SENSITIVE TO IONIZING RADIATION AND TO A RADIOMIMETIC CHEMICAL.

Scudiero DA, Meshell AN, Scarpinato RG, Meyer SA, Clatterbuck BE, Tarone RE, Robbins JH

Frederick Cancer Res. Center, P.O. Box B, Frederick, MD, 21701

J Invest Dermatol; 78(3):234-238 1982

Lymphoblastoid lines, derived by transforming peripheral blood lymphocytes with Epstein-Barr virus, and skin fibroblast lines were established from two patients with tuberous sclerosis. The number of viable lymphoblastoid cells was determined by their ability to exclude the vital dye trypan blue after their irradiation with x-rays or 254 nm ultraviolet light. The growth of fibroblasts was determined by their ability to form colonies after treatment with the radiomimetic, DNA-damaging chemical N-methyl-N'-nitro-N-nitrosoguanidine. The tuberous sclerosis lymphoblastoid lines were hypersensitive to x-rays but had normal sensitivity to the ultraviolet radiation. The tuberous sclerosis fibroblast lines were hypersensitive to the N-methyl-n'-nitro-N-nitrosoguanidine. The hypersensitivity of tuberous sclerosis cells to x-rays and to N-methyl-N'-nitro-N-nitrosoguanidine is believed to reflect defective repair of DNA damaged by these agents and may provide the basis for in vitro, including prenatal, diagnostic tests for tuberous sclerosis. (Author abstract) (51 Refs)

8. REPAIR AND REPLICATION OF DNA IN HEREDITARY (BILATERAL) RETINOBLASTOMA CELLS AFTER X-IRRADIATION.

Cleaver JE, Char D, Charles WC, Rand N

Lab. Radiobiology and Environmental Health, Univ. California, San Francisco, CA, 94143

Cancer Res; 42(4):1343-1347 1982

Fibroblasts from patients with hereditary retinoblastoma reportedly exhibit increased sensitivity to killing by x-rays. Although some human syndromes with similar or greater hypersensitivity to DNA-damaging agents (eg, x-rays, ultraviolet light, and chemical carcinogens), such as xeroderma pigmentosum, are deficient in DNA repair; most do not have such clearly demonstrable defects in repair. Retinoblastoma cells appear to be normal in repairing single-strand breaks and performing repair replication after x-irradiation and also in synthesizing poly(adenosine diphosphoribose). Semiconservative DNA replication in these cells, however, is slightly more resistant than normal after x-irradiation, suggesting that continued replication of damaged parental DNA could contribute to the pathogenesis of the disease. This effect is small, however, and may be a consequence rather than a cause of the fundamental enzymatic abnormality in retinoblastoma that causes the tumorigenesis. (Author abstract) (42 Refs)

9. RESISTANCE TO ULTRAVIOLET RADIATION IN HUMAN MELANOMA CELLS.

Konishi T

Second Dept. Internal Medicine, Mie Univ. Sch. Medicine, Tsu, Japan

Mie Med J; 31(1):15-27 1981

Sensitivities of four malignant melanoma (MM) cell lines, MM1M1, MM2MI, SK-Mel-28, and SK-Mel-37 to UV radiation were compared with those of normal human fibroblasts (NHF-2 and NHF-26), xeroderma pigmentosum cells (XP11MI), and HeLa S3 cells. Cell cultures were exposed to various doses of UV (254 nanometer, 1 Joule/square meter/

sec) and cultured for 2 wk. Assays of colony-forming ability indicated that MM1MI cells were more resistant to UV than HeLa S3 and NHF-2 cells. Comparison of thymine dimer content showed no significant differences between MM1MI, SK-Mel-28, and HeLa cells, indicating that the resistance of MM cells was not the result of a lower level of UV damage. Measurement of excision repair by the 5-bromo-2'-deoxyuridine (BrdUrd) photolysis technique showed no differences between MM cells and other types. Measurement of unscheduled DNA synthesis labeling showed variations in incorporation of [3H]thymidine from cell to cell but no significant differences overall. Analysis of postreplication repair using [3H]thymidine and BrdUrd indicated that MM cells carried out de novo synthesis more rapidly than HeLa cells. The wt-av mol wt of newly synthesized DNA was reduced in the presence of caffeine, indicating that DNA repair in MM cells is caffeine-sensitive, and to a greater degree than other cell types. Resistance of MM cells to UV is apparently due to a caffeine-sensitive DNA repair mechanism. (26 Refs)

BIOLOGICAL ASPECTS OF DNA ALTERATION AND REPAIR IN RELATION TO MUTAGENICITY

10. RELATIONSHIP BETWEEN THE GENETICALLY DETERMINED ACETYLATOR PHENOTYPE AND DNA DAMAGE INDUCED BY HYDRALAZINE AND 2-AMINOFLUORENE IN CULTURED RABBIT HEPATOCYTES.

McQueen CA, Maslansky CJ, Glowinski IB, Crescenzi SB, Weber WW, Williams GM
Div. Pathology and Toxicology, American Health Foundation, Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Proc Natl Acad Sci USA; 79(4,part1):1269-1272 1982

The relationship between acetylation rates of rabbit hepatocytes and their susceptibility to genotoxicity by DNA-damaging chemicals that undergo N-acetylation was studied in primary cultures of hepatocytes from New Zealand White rabbits that have a genetically determined difference in acetylation rates. Hepatocytes from rapid and slow acetylator rabbits maintained in culture the difference in acetylation rates that existed in vivo. DNA repair, an index of DNA damage, was produced by hydralazine in hepatocytes from slow acetylator rabbits but not in those from rapid acetylators. In contrast to these results, hepatocytes from rapid acetylators were more sensitive than those from slow acetylators to toxicity from the carcinogen 2-aminofluorene and displayed greater amounts of DNA repair. The amount of DNA repair measured with either chemical was dose dependent. These phenotype-dependent differences in the genoto xicity of two DNA-damaging chemicals provide evidence for the role of the acetylation polymorphism as a factor in determining susceptibility to toxicity, and perhaps carcinogenicity, of these chemicals. (Author abstract) (48 Refs)

11. CELL TRANSFORMATION AS A SYSTEM FOR STUDYING MECHANISMS OF CARCINOGENESIS.

Kakunaga T, Crow JD, Lo KY, Hamada H, Kirakawa T
Cell Genetics Section, Lab. Molecular Carcinogenesis, NCI, NIH, Bethesda, MD, 20205
Gann Monogr Cancer Res; 27:231-242 1982

Molecular evidence of mutation occurrence in a chemically-transformed cell is presented. The value and concept of an in vitro mammalian cell transformation system for studying carcinogenesis is discussed. Six subclones of BALB/3T3A31 cells which showed constant susceptibility to induced transformation through more than 50 cell generations were highly susceptible to UV irradiation (A31-1-13), intermediately sensitive (A31-1-1, A31-1-2, and A31-1-7), and resistant (A31-1-8 and A31-1-15). These cell variants were examined for the killing effects of carcinogens, transformation induction by chemical carcinogens, transformation by tumor viruses, induction of ouabain-resistance mutation, and type and amount of DNA adducts formed after treatment with chemical carcinogens and their rate of removal. The results suggest that mutations or DNA damage induced by carcinogens have nothing to do with transformation induction, or that the transformation process involves two steps: the mutational step and a step required for expression of the transformed phenotype. A procedure for isolating a recombinant DNA containing a DNA sequence complementary to a particular messenger RNA for molecular cloning is described. (38 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN VERTEBRATES

12. SITE-SPECIFIC MUTAGENESIS BY ERROR-DIRECTED DNA SYNTHESIS.

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Nature; 295(5851):708-710 1982

The use of misincorporation during DNA synthesis to create site-specific mutagenesis was attempted using single-stranded bacteriophage phiX174 circular DNA containing an amber mutation. The fragment HpaI2 (phiX174 positions 31-1,294) was obtained from phiX174 RF DNA by endonuclease cleavage. The 3'OH terminus of the fragment was elongated using DNA polymerase from Escherichia coli with deoxyATP (dATP) and deoxycytosine triphosphate (dCTP), which were complementary to the first three template positions. A second sunthesis phase utilized the error-prone DNA polymerase from avian myeloblastosis virus (AMV). Deoxynucleosides were used in three different combinations. After allowing for misincorporation, the subsequent correct nucleotide was inserted. The newly copied DNA was transfected into E coli, and the frequency of am18 mutations was determined. When dATP, which was complimentary to position 23 in the am18 region, was present during replication with AMV DNA polymerase, the reversion frequency was 4x that of uncopied template DNA. When dATP was not present, the reversion frequency was 100x times that of uncopied template DNA. Further experiments confirmed that reversions were caused by single-base substitutions. Thymine-guanine mispairing was more likely than thymine-thymine or thymine-cytosine mispairing. Results indicate that misincorporation can be used to create site-specific mutagenesis. (23 Refs)

13. EXCISION OF BENZO[A]PYRENE DIOL EPOXIDE I ADDUCTS FROM NUCLEOSOMAL DNA OF CONFLUENT NORMAL HUMAN FIBROBLASTS.

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Chem Biol Interact; 38(3):261-274 1982

The formation and removal of covalent adducts of racemic 7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy-7,8,9,10 tetrahydrobenzo[a]pyrene (BPDE I) was studied in nucleosomal DNA of confluent cultures of normal human fibroblasts (NF). For this purpose NF were prelabeled in their DNA with [14C]-thymidine and treated with [3H]BPDE I. The adducts were composed of 77% (7R)-N2-(7beta,8alpha,9alpha-trihydroxy-7,8,9,10 tetrahydrobenzo[a]pyrene-10-yl)deoxyguanosine, 12% of the corresponding 7S-enantiomer and of minor amounts of adducts to cytosine and adenine. The adduct composition did not change significantly in 24-hr post treatment incubation. Bulk mononucleosomes were prepared from micrococcal nuclease digested nuclei and their DNA analyzed by gel electrophoresis. The adduct concentrations were determined in 145 base pair (bp) nucleosomal core-DNA, 165 bp chromatosomal DNA and in total nuclear DNA. From these data the concentration in nucleosomal linker-DNA was calculated. The initial adduct distribution was non-random and 6.3 times higher in 47 bp linker-DNA relative to 145 bp core-DNA and 9.2 times higher in 27 bp linker-DNA relative to 165 bp chromatosomal DNA. Adduct removal was very rapid during the first 8 hr and more efficient from linker-DNA than from core-DNA. After this early phase the adducts located in 145 bp core-DNA became refractory to further excision and represent a major fraction of the adducts persisting in DNA of NF over a prolonged period. In contrast, further adduct removal was observed from nucleosomal linker-DNA. (Author abstract) (31 Refs)

14. FORMATION AND REMOVAL OF (GUAN-8-YL)-DNA-2-ACETYLAMINOFLUORENE ADDUCTS IN LIVER AND KIDNEY OF MALE RATS GIVEN DIETARY 2-ACETYLAMINOFLUORENE.

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NIH, Building 37, Room 3A19, Bethesda, MD, 21205
Cancer Res; 42(4):1317-1321 1982

Radioimmunoassay has been used to measure acetylated and deacetylated deoxyguano sine C-8 DNA adducts of 2-acetylaminofluorene in liver and kidney DNA of male Wistar-Furth rats fed a dietary regimen of 0.02 or 0.04% 2-acetylaminofluorene. When adduct formation was monitored during continuous feeding up to 60 days, substantial levels of binding (80 fmol/ug DNA) were observed in liver by 1 day, and maximum steady-state values averaging 230 fmol/ug DNA were reached by 30 days. Initially, during the continuous feeding, about 80% of the total C-8 adducts were deacetylated [N-deoxyguanosin(8-yl)aminofluorene], and this proportion increased to about 97% by 15 and 30 days of administration of 0.04 and 0.02% 2-acetylaminofluorene diets, respectively. Levels of C-8 adducts bound to kidney DNA in the same animals averaged 10 to 15% of the liver values with greater than or equal to 80% of these adducts in the deacetylated form. In separate experiments, rats were exposed to 2-acetylaminofluorene for 3, 7, 28, and 112 days; the carcinogen-containing diet was discontinued; and C-8 adducts were monitored during 1, 7, and 28 days of feeding control diet. At both carcinogen doses, after dietary administration for 3 or 7 days, there was a rapid decrease in liver C-8 adducts so that, after 28 days on control diet, 65 to 90% of the original adducts were no longer present in the DNA. In contrast, in animals fed 0.02% 2-acetylaminofluorescene for 28 days, there were high levels (70 to 100% of the original C-8 adduct) remaining on the DNA at the end of 28 days on control diet. This apparent loss in capacity for removal of C-8 adducts is discussed in relation to biological and biochemical changes induced in the rat liver during 2-acetylaminofluorene hepatocarcinogenesis. (Author abstract) (26 Refs)

15. RAPID RELEASE OF CARCINOGEN-GUANINE ADDUCTS FROM DNA AFTER REACTION WITH N-ACETOXY-2-ACETYLAMINOFLUORENE OR N-BENZOYLOXY-N-METHYL-4-AMINOAZOBENZENE.

Tarpley WG, Miller JA, Miller EC
McArdle Lab. Cancer Res., Univ. Wisconsin Medical Sch., Madison, WI, 53706
Carcinogenesis; 3(1):81-88 1982

Reaction of N-benzoyloxy-N-methyl-4-aminoazobenzene (N-benzoyloxy-MAB) or N-acetoxy-N-acetyl-2-aminofluorene (N-acetoxy-AAF), model ultimate aromatic amine or amide carcinogens, with [purine-14C]DNA at pH 7.4 or reaction of N-hydroxy-2-aminofluorene (N-hydroxy-AF) at pH 4.6 resulted in the rapid release of 14C-containing products not precipitable with the DNA. Four such products were obtained on reaction with N-acetoxy-AAF, two with N-hydroxy-AF, and six with N-benzoyloxy-MAB. Depending on the DNA sample used, the total amounts of 14C in these products from the reactions with N-benzoyloxy-MAB or N-acetoxy-AAF ranged from about 5% to as much as 30-40% of the amounts in the N-(deoxyguanosin-8-yl)-MAB or N-(deoxyguanosin-8-yl)-AAF residues in the DNA from the same reaction mixtures. Reactions with N-acetoxy-[a cetyl-3H]AAF showed that the two major products retained the amide residue from the N-acetoxy-AAF. when the reactions were carried out with [guanine-(8-3H; 8-14C); adenine-(2,8-3H; 8-14C)]DNA, the two major products formed from N-acetoxy-AAF and four products formed from N-benzoyloxy-MAB had very low 3H:14C ratios; these ratios were those expected for guanine derivatives which had lost the 8-3H. Studies on the major DNA adducts N-(deoxyguanosin-8-yl)-MAB and N-(deoxyguanosin-8-yl)-AAF indicated that the new adducts were not formed from these nucleosides. The data suggest that the two major AAF products and the four MAB adducts studied are guanine derivatives formed by depurination of N-7 substituted adducts in the DNA. (Author abstract) (49 Refs)

16. PERSISTANCE OF DNA ADDUCTS IN RAT LIVER AND KIDNEY AFTER MULTIPLE DOSES OF THE CARCINOGEN N-HYDROXY-2-ACETYLAMINOFLUORENE.

Beland FA, Dooley KL, Jackson CD
Natl. Center Toxicological Res., Food and Drug Admin., Jefferson, AR, 72079
Cancer Res; 42(4):1348-1354 1982

Male and female Sprague-Dawley rats were treated by gastric intubation either 1, 2, 3, or 4 times at biweekly intervals with 10-mg/kg doses of the hepatocarcinogen of N-[ring-3H]-hydroxy-2-acetylaminofluorene. Then either 1 or 14 days following the last treatment, the concentrations of 2-aminofluorene and 2-acetylaminofluorene adducts in liver and kidney DNA were established. 2-Acetylaminofluorene adducts were found in male rat liver DNA only. The C-8-acetylated adduct, N-(deoxyguanosin-8-yl)-2-acetylaminofluorene, was detected

only on the day following treatment at a concentration between 1.0 and 2.4 pmol/mg DNA. A second acetylated adduct, 3-(deoxyguanosin-N2-yl)-2-acetylaminofluorene, was found at both 1 and 14 days after treatment and, as a result, increased in concentration with repeated doses, from 0.2 pmol/mg DNA after one dose to 2.8 pmol/mg DNA after four treatments. The major adduct detected in male rat liver and the only adduct found in female rat liver and in kidney from either sex was N-(deoxyguanosin-8-yl)-2-aminofluorene. This adduct was slowly lost from the DNA and therefore increased in concentration with repetitive treatments as follows: male liver, 4.0 to 9.4 pmol/mg DNA; female liver, 11.4 to 30.6 pmol/mg DNA; male kidney, 1.1 to 1.8 pmol/mg DNA; and female kidney, 1.8 to 17.7 pmol/mg DNA. These data indicate that certain DNA adducts can accumulate in both target and non-target tissues and therefore suggest that persistence of DNA adducts per se is not sufficient for tumor induction. (Author abstract) (64 Refs)

17. EVIDENCE THAT POLY(ADP-RIBOSE)POLYMERASE IS INVOLVED IN THE LOSS OF NAD FROM CULTURED RAT LIVER CELLS.

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Biochem J; 202(2):551-553 1982

Rat hepatocytes cultured for 24 hr lose 60% of their NAD content. By using the differential response to inhibitors of the two major enzymes that catabolize NAD in mammalian cells, it is shown that poly(ADP-ribose) polymerase is responsible for the loss of NAD. The relevance of this observation to the use of cultured hepatocytes for the study of DNA repair induced by carcinogens is discussed. (Author abstract) (13 Refs)

18. POTENTIATION OF CELL KILLING BY INHIBITORS OF POLY(ADP-RIBOSE) POLYMERASE IN FOUR RODENT CELL LINES EXPOSED TO N-METHYL-N-NITROSOUREA OR UV LIGHT.

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Chem Biol Interact; 38(3):325-338 1982

The sensitivities (Do-values) of the cytotoxic effect of MNU on four rodent cell lines were: mouse L1210, 0.07 mM; rat Yoshida sarcoma, 0.52 mM; Chinese hamster V79A, 0.70 mM and the UV sensitive, x-ray sensitive V79/79, 0.35 mM. The abilities of maximum non-toxic doses of the poly(ADP-ribose) polymerase inhibitors, 5-methyl nicotinamide (5MeN), 3-methoxybenzamide (3MBA) and caffeine to potentiate this cytotoxicity and that of UV light in V79A and V79/79 was measured. The degree of potentiation (ratio Do without inhibitor/Do with inhibitor) was both agent and cell line dependent. In general the lymphoid cell lines L1210 and YS showed greater potentiation, up to four-fold, than did the fibroblast lines V79A and V79/79. The use of inhibitors in pairs suggested that 5MeN and 3MBA affect one process whereas caffeine affects additional processes. The data provide further support for a role for poly(ADP-ribose) in DNA repair, but indicate that metabolic factors may modify the effectiveness of individual inhibitors of poly(ADP-ribose)polymerase in different cell lines. (Author abstract) (40 Refs)

19. ACCUMULATION AND REPAIR OF SINGLE-STRAND DNA BREAKS IN PERIPHERAL BLOOD LYMPHOCYTES OF MICE OF DIFFERENT AGES EXPOSED TO GAMMA AND UV RADIATION.

Malakhova LV, Fomenko LA

Inst. Biological Physics, Pushchino, USSR

Radiobiologia; 21(6):903-906 1981

Repair of gamma and UV radiation-induced single-strand DNA breaks was studied in peripheral blood lymphocytes of 2-mo-old and 15-17-mo-old A/He and C3H/Sn mice. The repair of gamma radiation-induced DNA breaks did not depend upon the age, while the repair of UV-induced single-strand breaks in young mice was more effective than that in older mice. These findings indicate that the decreased rate of excision of UV-induced DNA breaks and reduced level of unscheduled DNA synthesis are associated with the decrease in the number of substrate sites during the aging. (7 Refs) (In RUS)

20. EFFECTS OF DELAYS IN THE CELL CYCLE ON THE INDUCTION OF PRENEOPLASTIC AND NEOPLASTIC LESIONS IN RAT LIVER BY 1,2-DIMETHYLHYDRAZINE.

Ying TS, Enomoto K, Sarma DS, Farber E

Dept. Pathology, Univ. Toronto, Toronto, Ontario M5G 1L5, Canada

Cancer Res; 42(3):876-880 1982

This study was designed to explore further the relationship between cell proliferation and the induction of early putative preneoplastic lesions by carcinogens. Rats were given a non-necrogenic dose of 1,2-dimethylhydrazine 24 hr before being subjected to partial hepatectomy. Beginning 4 hr later, hydrocortisone was injected 10x at 4-hr intervals to delay progression through the cell cycle, including inhibition of DNA synthesis by at least 85% for about 40 hr. At the appropriate time thereafter, the putative preneoplastic hepatocytes were selectively stimulated to grow in vivo into gamma-glutamyltransferase-positive focal lesions. Animals given hydrocortisone showed a large decrease (71%) in the number of gamma-glutamyltransferase-positive foci. In contrast, when hydrocortisone was given at 6 days after partial hepatectomy, no inhibition in the induction of hepatic lesions was observed. In the next experiments, rats were treated with 1,2-dimethylhydrazine and were subjected to partial hepatectomy at 12, 24, or 84 hr or 1 wk thereafter. A significant number of gamma-glutamyltransferase-positive foci was found when partial hepatectomy was performed at 12 or 24 hr but far fewer were found when the operative partial hepatectomy was delayed to 48 hr or 1 wk later. Similarly, in long-term experiments, 6 of 14 animals developed primary hepatocellular carcinoma 13 mo after the time of injection of 1,2-dimethylhydrazine when partial hepatectomy was performed at 12 hr, while none of the animals developed liver cancer when the operation was performed at 48 hr. These results imply that the majority of biochemical lesions induced by 1,2-dimethylhydrazine that are relevant to the induction of liver preneoplasia and neoplasia are short-lived and that their persistence is associated with some cellular activity closely related to the cell cycle. (Author abstract) (39 Refs)

21. THE EXTENT OF BONDING OF NEWLY SYNTHESIZED DNA TO PARENT TEMPLATE IN UNIRRADIATED CELLS AS A PREDICTION OF RADIATION SENSITIVITY.

Cramp WA, Lunec J, George A, Cresswell S, Lewis PD, Chamberlain S, Harris G, Olsen I
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Int J Radiat Biol; 41(2):193-196 1982

Hydroxylapatite chromatography was used to measure the amount of single-stranded DNA after a short pulse of the radio-labelled DNA precursor base thymidine to mammalian cells in log phase growth. Mammalian cells studied consisted of the following: V79 Chinese hamster lung fibroblasts, L5178YR and L5178YS resistant and sensitive mouse lymphomas, EA Ehrlich ascites cells, NHSF normal human skin fibroblasts, LDV human lymphoid cells, CL Chang human liver cells, HeLa human carcinoma cells, FASF skin fibroblasts from Friedreich's ataxia patients, ATSF skin fibroblasts from Friedreich's ataxia patients, and ATSF skin fibroblasts from ataxia telangiectasia patients. (11 Refs)

22. CORRELATION BETWEEN INACTIVATION OF HUMAN CELLS AND NUMBERS OF PYRIMIDINE DIMERS INDUCED BY A SUN LAMP AND 254 NM RADIATION.

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Dept. Biological Sciences, Wright State Univ., Dayton, OH, 45435
Photochem Photobiol; 35(2):269-274 1982

Nondividing human fibroblasts are inactivated by radiation from a source (a Westinghouse sun lamp) that simulates the UV spectrum of sunlight. Survival curves determined for a DNA excision repair-proficient and a repair-deficient strain (XP12BE) are related to those determined using germicidal light (254 nm) by constant fluence modification factors. In addition, the same fraction of XP12BE cells are killed per pyrimidine dimer by 254 nm and sun lamp light. These results, when related to other survival and photoreactivation studies, suggest that the mechanism for inactivation of nondividing human cells by sun lamp light is the same as that by 254 nm and that pyrimidine dimers are the major responsible photolesion. Repair reverses some of the lethal effects of this light. We suggest that these conclusions apply to sunlight-irradiated skin cells in vivo. (Author abstract) (26 Refs)

23. REJOINING OF DNA STRAND BREAKS AFTER GAMMA-IRRADIATION IN CULTURED FISH CELLS, CAF-MM1.

Mitani H, Egami N
Zoological Inst., Faculty Science, Tokyo Univ., Tokyo 113, Japan
Int J Radiat Biol; 41(1):85-90 1982

Induction and repair kinetics of DNA strand breaks in cultured fish cells (CAF-MM1), from the fin of the goldfish Carassius auratus, and in mouse L cells were compared. DNA strand separation methods under mild alkaline conditions and separation with in hydroxylapatite chromatography were used to determine if the kinetic factors correlate with differences in radiosensitivity. The amount of DNA strand breakage immediately after irradiation was almost the same in the mouse L cells and in CAF-MM1 cells in spite of their large difference in radiosensitivity. The iniital DNA strand breaks were able to rejoin during further incubation at 26 C, but this process was inhibited at 4 C in CAF-MM1 cells. The amount of residual DNA strand breaks 7 hr after irradiation was higher in the CAF-MM1 cells than in the mouse L cells, and the residual DNA strand breaks did not correlate with the radiosensitivity of the CAF-MM1 and mouse L cells. (19 Refs)

24. EVIDENCE FOR A FAST REPAIR OF APURINIC SITES INDUCED BY N-NITROSO-DIMETHYLAMINE IN RAT LIVER DNA.

Parodi S, Taningher M, Balbi C, Pala M, Santi L
Istituto di Oncologia, Universita di Genova, Genova, Italy
Ital J Biochem; 30(5):375-387 1981

Evidence for a fast repair of apurinic sites induced by N-nitroso-dimethylamine in rat liver DNA is presented. Determination of the number of single stranded breaks after different incubation periods in alkali showed that most were alkali-labile sites, with a half-life of approx 33 min. (24 Refs)

25. INACTIVATION OF NUCLEOTIDE EXCISION REPAIR IN CHINESE HAMSTER OVARY CELLS BY EXPOSURE TO AN ALKYLATING AGENT.

Park SD, Cleaver JE
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Photochem Photobiol; 35(3):419-421 1982

Unscheduled DNA synthesis and excision of pyrimidine dimers in Chinese hamster ovary cells irradiated with UV light were inhibited by prior exposure to the alkylating agent N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) (1-10 uM). Although the pathways for excision of pyrimidine dimers and alkylation damage are known to differ, alkylations from MNNG exposure appear to have a direct effect on the nucleotide excision repair system. These results indicate that the method of exposing cells to two DNA-damaging agents to determine whether they are repaired by common or different pathways can be quite unreliable because of other effects on the repair systems themselves. (Author abstract) (27 Refs)

26. APHIDICOLIN PROMOTES REPAIR OF POTENTIALLY LETHAL DAMAGE IN IRRADIATED MAMMALIAN CELLS SYNCHRONIZED IN S-PHASE.

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Biochem Biophys Res Commun; 104(4):1209-1214 1982

The effect of aphidicolin on radiation damage was studied in mouse Ehrlich ascites tumor cells grown in suspension in vitro and synchronized in the S-phase of growth. Cells were irradiated with either 140 kilovolt x-rays (6 hr) or 254 nanometer UV (12 hr). Irradiated cells were treated with 0.5 ug/ml aphidicolin for 6 hr and then plated. After irradiation with x-rays, a higher survival of cells was noted in aphidicolin-treated cells than in cells plated immediately after irradiation. An intermediate effect on survival was noted in x-irradiated cells incubated in basal salt soln (BSS) for 6 hr before plating. In UV irradiated cells, extent of repair was not as great as that for cells treated with BSS for 12 hr before plating. The results show that aphidicolin, at 0.5 ug/ml, promotes repair of potentially lethal damage (PLD) after irradiation by both x-rays and UV. The possible involvement of alpha polymerase and beta polymerase in repair of PLD is discussed. (21 Refs)

27. NATURE AND REPAIR OF POTENTIALLY LETHAL INJURIES.

Gotlib VIa, Synzynys BI, Trofimova SF, Noskin LA, Saenko AS, Pelevina II
Inst. Chemical Physics, Moscow, USSR
Radiobiologia; 21(6):818-828 1981

The nature of potentially lethal injuries (PLI) was studied in cultured LL cells irradiated with gamma rays or treated with methylnitrosourea (MNU). Cells irradiated with 600 rads showed repair of PLI; short-term exposure to nontoxic concentrations of the inhibitor of DNA synthesis enhanced the repair of PLI. Elimination of single-stranded DNA breaks after irradiation with 6,000 rads was more effective in the conditioned medium. The repair of double-stranded DNA breaks induced by MNU was observed only in the complete medium. The absence of repair of double-stranded DNA breaks was correlated with the absence of repair of PLI. (40 Refs) (In RUS)

28. DIFFERING LEVELS OF EXCISION REPAIR IN HUMAN FETAL DERMIS AND BRAIN CELLS.

Gibson RE, D'Ambrosio SM
Dept. Radiology, Ohio State Univ. Comprehensive Cancer Center, Coll. Medicine, Ohio State Univ., Columbus, OH, 43210
Photochem Photobiol; 35(2):181-185 1982

The levels of DNA excision repair, as measured by unscheduled DNA synthesis (UDS) and the UV-endonuclease sensitive site assay, were compared in cells derived from human fetal brain and dermal tissues. The level of UDS induced following ultraviolet (UV) irradiation was found to be lower (approx 60%) in fetal brain cells than in fetal dermal cells. It was determined, using the UV-endonuclease sensitive site assay to confirm the UDS observation, that 50% of the dimers induced by UV in fetal dermal cells were repaired in 8 hr, while only 15% were removed in the fetal brain cells during the same period of time. Even after 24 hr, only 44% of the dimers induced by UV in the fetal brain cells were repaired, while 65% were removed in the dermal cells. These data suggest that cultured human fetal brain cells exhibit lower levels of excision repair compared to cultured human fetal dermal cells. (Author abstract) (31 Refs)

29. DNA REPAIR AFTER GAMMA RADIATION AND SUPEROXIDE DISMUTASE ACTIVITY IN LYMPHOCYTES FROM SUBJECTS OF FAR ADVANCED AGE.

Licastro F, Franceschi C, Chiricolo M, Battelli MG, Tabacchi P, Cenci M, Barboni F, Pallenzona D
Inst. General Pathology, Univ. Bologna, Via S. Giacomo 14, 40126 Bologna, Italy
Carcinogenesis; 3(1):45-48 1982

DNA repair after gamma radiation was studied in purified T lymphocytes from young and aged subjects. Two different assays were employed. In the first, T lymphocytes were stimulated with phytohemagglutinin (PHA) for 72 hr and then treated with hydroxyurea, irradiated with 30 K rads and pulsed with [3H]thymidine (TdR) for 4 hr. In the second, T lymphocytes were first irradiated with graded doses of gamma rays (200-800 rads) and then stimulated with PHA, cultured for 72 hr and pulsed with 3H-TdR for the last 6 hr of culture. T lymphocytes from aged subjects showed a lack of DNA repair synthesis in the first assay whereas only minor differences were found in the second assay between the two groups, ie, a certain degree of radioresistance in aged lymphocytes. Lymphocyte superoxide dismutase activity showed great individual variations in both groups and a slight increase in old subjects. (Author abstract) (44 Refs)

30. UNSCHEDULED DNA SYNTHESIS INDUCED BY N-METHYL-N'-NITRO-N-NITROSOGUANIDINE IN HELA CELLS.

Yamada K, Kato H, Hanaoka F, Yamada M
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Gan; 73(1):63-69 1982

N-Methyl-N'-nitro-N-nitrosoguanidine (MNNG)-induced repair (unscheduled) DNA synthesis was studied in intact HeLa cells as well as in the cell lysate. The incorporation of dTTP[methyl-3H] in vitro by the cell lysate was dependent on the dose of MNNG, and was linear for 2 min, reaching the maximum at 4 min. The optimum conditions were the same as for UV-induced in vitro repair synthesis. The presence of hydroxyurea and arabinofuranosyl cytosine during in vivo incubation with MNNG was necessary for enhancement of in vitro DNA synthesis. This MNNG-induced in vitro DNA synthesis was inhibited by aphidicolin, but not by 2',3'-dideoxythymidine-5'-triphosphate. It thus appears that DNA polymerase alpha participates in MNNG-induced unscheduled DNA synthesis in vitro. (Author abstract) (25 Refs)

31. REASSOCIATION OF HUMAN LYMPHOBLASTOID CELL DNA REPAIR REPLICATED FOLLOWING METHYL METHANESULFONATE TREATMENT.

Meltz ML, Whittam NJ, Thornburg WH
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Chem Biol Interact; 39(1):77-88 1982

The reassociation rates of repair replicated DNA of two human lymphoblastoid cell lines, the WIL2-A3 'normal' line and the RAJI line of Burkitt's lymphoma, were examined using the DNA/DNA 'C0t' hybridization technique. The cells were treated with methyl methanesulfonate (MMS), an alkylating agent and mutagen, to induce the repair. The incorporated repair replication radioactivity in highly repetitive sequences of WIL2-A3 cell DNA reassociates as expected for a randomly distributed incorporation. The reassociation of repair radioactivity in sequences of fewer numbers of copies, however, is less than expected for a random distribution. It is less than that occurring for semiconservatively synthesized DNA of WIL2-A3 cells co-incubated with the repair labeled DNA as an internal control. The observed difference could be due to an over-representation of repair replication radioactivity in DNA sequences with fewer copies. It is unlikely to be due to residual alkali labile damage resulting from MMS treatment, since a similar difference was not observed when semiconservatively labeled DNA from cells which had been treated with MMS for the same time and at the same concentration as in the repair experiments was substituted for repair replicated DNA in the reassociation reactions. Other possible causes of the apparent difference in the reassociation rates observed are discussed. (Author abstract) (17 Refs)

32. APPLICATION OF ARABINOFURANOSYL CYTOSINE IN THE KINETIC ANALYSIS AND QUANTITATION OF DNA REPAIR IN HUMAN CELLS AFTER ULTRAVIOLET IRRADIATION.

Snyder RD, Carrier WL, Regan JD
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Biophys J; 35(2):339-350 1981

Three-hr pulses of arabinofuranosyl cytosine (ara-C) and hydroxyurea were used to analyze the kinetics of human fibrob-

last DNA repair after UV irradiation; 57-100% of pyrimidine dimer sites undergoing repair were detected. The analysis allowed insights into both the nature of the ara-C inhibitory effect and the nature of the repair event itself. (33 Refs)

33. A MODEL FOR THE EFFECT OF EXCISION REPAIR ON THE SURVIVAL OF HUMAN CELLS EXPOSED TO CHEMICAL CARCINOGENS.

Miller JH, Heflich RH
Pacific Northwest Lab., Richland, WA, 99352
Chem Biol Interact; 39(1):45-55 1982

A model is presented which correlates the survival of normal human fibroblasts (NF) after exposure to N-acetoxy-2-acetylaminofluorene (N-AcO-AAF) with the rate of excision of carcinogen residues bound to DNA. Measurements of the rate of excision of carcinogen residues suggest that this is a first-order process with 37% of the adducts remaining after about 70 hr. From this information and the dose-response relationship for survival of NF and repair deficient cells we can determine the mean number of adducts required to produce a potentially lethal lesion and the effective time available for repair. When these adjustable parameters have been determined, we can use the model to predict the rate of excision in partially repair-deficient cells and the effect of extending the repair period by arresting cell growth after treatment. Survival studies in which cells were held at confluence for varying amounts of time between treatment and replating at low density show good agreement with the predictions of the model. (Author abstract) (14 Refs)

34. RECOVERY AFTER EXPOSURE TO NEAR-ULTRAVIOLET LIGHT OF CELLS CONTAINING 5-BROMODEOXYURIDINE.

Hagan MP, Elkind MM
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Biophys J; 34(3):367-374 1981

Effects of near-UV irradiation were examined in synchronized Chinese hamster cells pulse-labeled with bromodeoxyuridine at times in the cell cycle when a shoulder-type survival curve appeared. Such cells were able to repair sublethal damage and potentially lethal damage expressed by caffeine. Kinetics of the two processes differed. In template-labeled cells, time is apparently inadequate to effect prereplication repair; effective contributions to cell survival from other types of DNA repair processe s are precluded. (19 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN INVERTEBRATES AND LOWER EUKARYOTES

35. CHARACTERIZATION OF POSTREPLICATION REPAIR IN SACCHAROMYCES CEREVISIAE AND EFFECTS OF RAD6, RAD18, REV3 AND RAD52 MUTATIONS.

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MGG; 184(3):471-478 1981

Postreplication repair of nuclear DNA was examined in an excision defective haploid strain of yeast lacking mitochondrial DNA (rad1 p(0)). The size of the DNA synthesized in cells exposed to various fluences of ultraviolet light (UV) corresponds approximately to the av interdimer distance in the parental DNA. Upon further incubation of cells following exposure to 2.5 J/m2, the DNA increases in size; by 4 hr, it corresponds to DNA from uniformly labeled cells. The alkaline sucrose sedimentation pattern of DNA pulse labeled at various times after UV irradiation, for up to 4 hr, does not change substantially, indicating that dimers continue to block DNA replication. A significant amount of postreplication repair requires de novo protein synthesis, as determined by its inhibition by cycloheximide. The rad6 mutant does not carry out postreplication repair, the rad18 and rad52 mutants show great inhibition while the rev 3 mutation does not affect postreplication repair. Both recombinational and nonrecombinational repair mechanisms may function in postreplication repair and most of postreplication repair is error free. (Author abstract) (54 Refs)

36. RECOMBINATION AND MUTAGENESIS IN RAD6 MUTANTS OF SACCHAROMYCES CEREVISIAE: EVIDENCE FOR MULTIPLE FUNCTIONS OF THE RAD6 GENE.

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MGG; 184(3):410-415 1981

The rad6-1 and rad6-3 mutants are highly UV sensitive and show an increase in spontaneous and UV induced mitotic heteroallelic recombination in diploids. Both rad6 mutants are proficient in spontaneous and UV induced unequal sister chromatid recombination in the reiterated ribosomal DNA sequence and are deficient in UV induced mutagenesis. In contrast to the above effects where both mutants appear similar, rad6-1 mutants are deficient in sporulation and meiotic recombination whereas rad6-3 mutants are proficient. The differential effects of these mutations indicate that the RAD6 gene is multifunctional. The possible role of the RAD6 gene in error prone excision repair of UV damage during the G1 phase of the cell cycle in addition to its role in postreplication repair is discussed. (Author abstract) (41 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN BACTERIA

37. PHOTOREACTIVATION AND EXCISION REPAIR OF UV INDUCED PYRIMIDINE DIMERS IN THE UNI CELLULAR CYANOBACTERIUM GLOEOCAPSA ALPICOLA (SYNECHOCYSTIS PCC 6308).

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Photochem Photobiol; 35(3):359-364 1982

The survival curve obtained after UV irradiation of the unicellular cyanobacterium Synechocystis is typical of a DNA repair competent organism. Inhibition of DNA replication, by incubating cells in the dark, increased resistance to the lethal effects of UV at higher fluences. Exposure of irradiated cells to near ultraviolet light (350-500 nm) restored viability to pre-irradiation levels. In order to measure DNA repair activity, techniques have been developed for the chromatographic analysis of pyrimidine dimers in Synechocystis. The specificity of this method was established using a haploid strain of Saccharo-

myces cerevisiae. In accordance with the physiological responses of irradiated cells to photoreactivating light, pyrimidine dimers were not detected after photoreactivation treatment. Incubation of irradiated cells under non-photoreactivating growth conditions for 15 hr resulted in complete removal of pyrimidine dimers. It is concluded that Synechocystis contains photoreactivation and excision repair systems for the removal of pyrimidine dimers. (Author abstract) (29 Refs)

38. REPAIR OF ULTRAVIOLET-DAMAGED TRANSFORMING DNA IN A MISMATCH REPAIR-DEFICIENT STRAIN OF HAEMOPHILUS INFLUENZAE.

Bagci H, Stuy JH
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Photochem Photobiol; 35(3):331-335 1982

Ultraviolet inactivation of Haemophilus influenzae transforming DNA followed inverse square root kinetics in both mismatch repair-proficient (hex) and deficient (hex-1) recipients. No DNA concentration effect was seen with UV-excision repair-deficient (uvr-) strains. Low-efficiency genetic markers remained more sensitive than high-efficiency ones when they were assayed on excision repair-deficient hex uvr- strains. They were equally resistant when hex- uvr- recipients were used. We explain this by assuming that recombinational repair of UV lesions in the donor strand and mismatch repair of the recipient strand may overlap and cause double strand interruptions. This will eliminate low-efficiency transformants. (Author abstract) (35 Refs)

39. ULTRAVIOLET SENSITIVITY OF THE ADDITION, DELETION AND REPLACEMENT OF LONG NONHOMOLOGOUS DNA SEGMENTS BY GENETIC TRANSFORMATION OF HAEMOPHILUS INFLUENZAE.

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Photochem Photobiol; 35(3):337-341 1982

We have recently described the construction and some properties of Hemophilus influenzae Rd strains with long and different R plasmid-derived DNA segments (nonhomologous inserts) at the same site in the HP1 prophage. These inserts can be added to a recipient's genome by genetic transformation, they can be deleted from the recipient genome, or they can be replaced by another insert. We report here that the UV inactivation of all three phenomena followed single hit kinetics. Deletion was roughly 10x more resistant; its UV-sensitivity equaled that of a high-efficiency point mutation. There was an inverse correlation between UV-sensitivity and additive transformation efficiency of the various inserts; sensitivity may thus be a measure of insert size. This correlation was not seen for deletion. All three phenomena were more sensitive when they were measured on excision repair-deficient uvr- recipients. The dose-reduction factor for addition was about 1.5 while it was about 2.6 for deletion. (Author abstract) (10 Refs)

40. POST REPLICATION REPAIR IN AN EXCISION DEFECTIVE STRAIN OF ESCHERICHIA COLI FOLLOWING TREATMENT WITH CIS DICHLORODIAMMINEPLATINUM(II).

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Biochem Biophys Res Commun; 104(2):693-700 1981

Alkaline sucrose density gradient centrifugation was used to determine the size of the DNA synthesized after treatment of the excision-defective mutant AB 2500 uvr A6 of Escherichia coli with cis-dichlorodiammineplatinum(II) (cisPDD) at 5, 15, or 30 ug/ml for 1 hr. Exposure to UV light yielded DNA with a reduced mol wt of about 12 x 10(6) daltons, compared to 10(8) daltons for the control. A similar concentration-dependent effect on DNA size was evident after cis-PDD treatment, with DNAs of about 28 x 10(6) daltons being produced after 30 ug/ml cis-PDD treatment. During post-treatment incubation the size of DNA increased in cis-PDD-treated cultures as indicated by the sedimentation profile, suggesting that single strand gaps or breaks had been caused by treatment but were rejoined during post-treatment incubation. The reduction in DNA size caused by cis-PDD is probably due to a delayed replication caused by binding of the compound to DNA. The return toward control-sized DNA during post-treatment suggested that a process similar to post-replication repair was at work. (20 Refs)

41. INDUCED RADIORESISTANCE: AN ASPECT OF INDUCED REPAIR.

Pollard EC, Fluke DJ, Kazanis D
Zoology Dept., Duke Univ., Durham, NC, 27706
MGG; 184(3):421-429 1981

Irradiation of Escherichia coli cells with UV or x-rays followed by incubation under conditions in which protein synthesis can occur results in a population of cells that is resistant to x-rays; however, this resistance develops only if the cells are recA and lexA, a fact that associates the phenomenon with induced (SOS) repair. By observing separately the component of a culture that is resista nt and the component that retains its normal growth, the fraction of induced and uninduced cells for a dose of UV or x-rays can be estimated. Such estimates show that the dose-response for UV induction of resistant cells agrees with that of the recA gene product. Thus induced radioresistance is considered to be due to the changes in the cell occasioned by the derepression of recA and lexA. These changes are expected to be involved with the synapsis of homologous genomes that is necessary for the use of a second genome to repair damage occurring in both strands of a duplex at the same base, as exemplified by a double-strand break or an inter-strand crosslink. This consideration is additionally supported by the increased resistance of cells grown to contain multiple genomes in the same envelope, an increased resistance not found in recA- or lexA- cells. The condition of a completed chromosome is also resistant, again not in recA- or lexA- cells. We suggest that cell killing by x-rays is due to the double-strand breaks which are not repaired by molecular synapsis before the arrival of the replication polymerase at the break. (Author abstract) (22 Refs)

MACROMOLECULAR BINDING OF CARCINOGENS

42. REACTIONS OF VINYL CHLORIDE WITH RNA AND DNA OF VARIOUS MOUSE TISSUES IN VIVO.

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Arch Toxicol; 49(2):117-129 1982

The irreversible binding of 14C-vinyl chloride metabolites to RNA and DNA of mouse brain, lung, liver, kidney, spleen, pancreas, and testes after a single ip injection has been studied. Hydrolysates of nucleic acids from selected organs were separated on Aminex A6 for quantitation of alkylation products. Radioactivity in nucleic acids was registered in all of the studied organs with the exception of brain. RNA from spleen, pancreas and liver, and DNA from spleen and liver contained the highest amounts of radioactivity. In nucleic acids from spleen and pancreas, both organs of high metabolic activity, the entire radioactivity was found metabolically incorporated as C1-fragments. In RNA of kidney and liver, a large part of the radioactivity was also present as incorporated C1-fragments, but 3,N4-ethenocytidine (in kidney) as well as 1,N6-ethenoadenosine and 1,N6-ethenoadenine (in kidney and liver) were identified as alkylation products. In liver DNA, incorporation of C1-fragments was insignificant, indicating different interactions of vinyl chloride metabolites (C1-fragments and alkylating products) with RNA and DNA. The elution profiles of radioactivity in hydrolysates of liver DNA were dominated by an alkylation product of unknown structure (probably a derivative of deoxyguanosine). Possibly, 1,N6-ethenodeoxyadenosine and 1,N6-ethenoadenine were also present in liver DNA. The results are consistent with the ability of viny c hloride to act as a multipotent carcinogen by alkylation of DNA in several tissues. (Author abstract) (45 Refs)

43. XANTHINE OXIDASE CATALYZED BINDING OF 1-NITROPYRENE TO DNA.

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Biochem Biophys Res Commun; 104(2):727-732 1981

Incubation of (4,5,9,10-3H)1-nitropyrene (1-NP: 20uM) with 2 mg/ml calf thymus DNA, xanthine oxidase (XO: 0.5 U/ml), and hypoxanthine (HX: 3.7 milliM) resulted in XO and HX becoming covalently bound to the DNA. The binding was linear for approx 30 min and reached a plateau at 120 min, with an estimated final binding level of 200-250 adducts/10(6) nucleotides. Adduct formation increased as enzyme concentration increased; it decreased in a concentration-dependent manner in response to the specific XO inhibitor allopurinol. Nitroreduction of 1-NP yields a species which readily reacts with DNA; the activity may be the basis of the compound's observed mutagenicity in bacteria. (23 Refs)

44. SOLUBILIZATION OF THE CARCINOGEN NICKEL SUBSULFIDE AND ITS INTERACTION WITH DEOXYRIBONUCLEIC ACID AND PROTEIN.

Lee JE, Ciccarelli RB, Jennette KW
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Biochemistry; 21(4):771-778 1982

Significant concentrations (1-10 mM) of nickel(II) were found in soln after incubation of the potent carcinogen nickel subsulfide in 0.05 M Tris-HCl, pH 7.4, solutions containing DNA, rat liver microsomes, and NADPH. The presence of NADPH decreased the rate of solubilization of nickel subsulfide. The solubilized nickel exhibited electronic absorption spectra and magnetic moments characteristic of octahedral nickel(II). The solubilized nickel(II) bound to DNA with an apparent equilibrium constant of 730 M-1 and with a saturation binding value of one nickel per 2.4 nucleotides. Microsomes lowered the saturation binding of nickel to DNA but dramatically increased the amount of nickel-DNA complex stable to precipitation with salt and poly-(ethylene glycol). The amount of protein associated with DNA precipitated from protein-extracted solutions correlated with the amount of nickel bound to DNA. These results suggest that microsomes mediate the binding of nickel to DNA by forming a stable ternary protein-nickel(II)-DNA complex. (Author abstract) (60 Refs)

45. CORRELATION BETWEEN THE ASSOCIATION AND THE DESMUTAGENICITY OF BENZO(A)PYRENE BY HEMIN: COMPARISON WITH HEMOPROTEINS, TRANSIENT METALS AND AMINES.

Yagi M, Akagawa S
Dept. General Education (Physics Lab.), Tokyo Medical and Dental Univ., Ichikawa, Chiba, 272, Japan
Cancer Biochem Biophys; 5(3):175-181 1981

Benzo(a)pyrene (BP) binding was accomplished in methanol:H20 (3:1) for 10 min on thin-layer chromatography plates with the following compounds: beef hemin, beef methemoglobin, human oxyhe moglobin, beef liver catalase, p-phenylenediamine (pPDA), hydroxylamine, 3,3'-diaminodipropylamine (DADPA), cupric chloride, and ferric chloride. After binding, unbound BP was removed and its concentration determined by fluorescence in dimethyl sulfoxide soln. Association constants (Kass) of BP with hemin and other compounds were determined by an equation relating the difference between free and bound fluorescence intensities. Mutation assay was by a modified Ames method with Salmonella typhimurium strain TA100; a desmutagenicity constant (Kmut) was calculated by a similar difference method. The loss of mutagenicity of BP was caused by binding with materials containing ferric but not ferrous iron. Kass and Kmut were, respectively, 8.5 x 10(4) and 7.0 x 10(4) for hemin and 2.2 x 10(3) and 2.3 x 10(3) for DADPA. The respective figures for other compounds were both less than 1,000 (FeCL3, pPDA) or differed by a large amount (CuCl2, hydroxylamine). (20 Refs)

46. INFLUENCE OF COENZYME A ON THE IN VITRO BINDING OF BENZO(A)PYRENE METABOLITES TO PROTEIN.

Raha CR, Gallagher CH, Reeve VE
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Res Commun Chem Pathol Pharmacol; 35(2):329-332 1982

Incubation of 20,000 x g supernatants of liver homogenates from female Wistar rats with benzo(a)pyrene (BP) and other cofactors in the presence of coenzyme A (CoA) produced metabolites that required extensive hydrolysis successively in 2N NaOH, 2N HCl, 2N NaOH and 6N HCl for their release. It is suggested that coenzyme A activated benzpyrenyl-amino acid formed via epoxide(s). The activated amino acid(s) became bound to thiol protein. (Author abstract) (6 Refs)

47. METABOLISM OF POLYCYCLIC AROMATIC HYDROCARBONS AND COVALENT BINDING OF METABOLITES TO PROTEIN IN RAT ADRENAL GLAND.

Montelius J, Papadopoulos D, Bengtsson M, Rydstrom J
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Cancer Res; 42(4):1479-1486 1982

The metabolism of the carcinogenic and adrenocorticolytic polycyclic aromatic hydrocarbon 7,12-dimethylbenz(a)anthracene in rat adrenals was investigated. Both 7,12-dimethylbenz(a)anthracene and benzo(a)pyrene, which also is a well-known carcinogen but has no short-term effects on rat adrenals, appear to be metabolized by one common type of cytochrome P-450-dependent monooxygenase localized in the endoplasmic reticulum. Studies of the kinetic properties of this cytochrome P-450 reveal that the Km values for 7,12-dimethylbenz(a)anthracene and benzo(a)pyrene are lower than 3 uM. Identification of metabolites indicates that, with both 7,12-dimethylbenz(a)anthracene and benzo(a)pyrene, phenols and diols were formed the relative rates of formation of which were markedly influenced by the epoxide s hydrase inhibitor cyclohexane oxide, suggesting that epoxides are intermediate metabolites. Added or endogenous microsomal glutathione S-transferase B had little or no effect on the distribution of metabolites. A rather selective binding of metabolites of 7,12-dimethylbenz(a)anthracene to soluble and microsomal proteins was demonstrated. The adrenal cytochrome P-450 involved in the conversion of these polycyclic aromatic hydrocarbons appears to be unrelated to those responsible for the synthesis of mineralocorticoids and glucocorticoids from cholesterol. Among androgens and estrogens, estradiol proved to be the most inhibitory steroid, suggesting a role of the hydrocarbon-metabolizing cytochrome P-450 in estrogen biosynthesis. However, no such function could be demonstrated conclusively. The metabolite patterns and the effects of nonsteroid inhibitors of liver monooxygenases, eg, alpha-naphthoflavone, SU 9055, and ellipticine, suggest that the properties of this cytochrome P-450 resemble those of the 3-methyl-cholanthrene-inducible cytochrome P-488 from rat liver. (Author abstract) (58 Refs)

48. BINDING OF CHLOROFORM TO MOUSE AND RAT HEMOGLOBIN.

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Health Effects Res. Lab., U.S. Environmental Protection Agency, Cincinnati, OH, 45268
Chem Biol Interact; 39(1):89-99 1982

The covalent binding of chemical carcinogens and mutagens to hemoglobin has been proposed as a dose monitor for environmental exposure. The binding of chloroform to hemoglobin in rats was demonstrated to result from the formation of addition adducts to amino acids in the globin. The altered amino acids were isolated with an amino acid analyzer employing ion exchange chromatography. The covalent binding of orally-administered [14C]chloroform to rat hemoglobin reached a peak within 10 hr. Afterwards, the amount of chloroform bound decreased slowly with half remaining at 7 wk. The extent of chloroform binding was linearly dependent upon dose between 0.1 and 100 umol/kg. Above 100 umol/kg chloroform the binding to hemoglobin increased at a reduced rate. The extent of [14C]chloroform binding resulting from either 10 daily dose of 0.1 umol/kg or a single 1.0 umol/kg was similar. The binding to hemoglobin in three strains of mice and rats varied from 85 -7 umol/g Hb for Swiss (CFN) mice to 152 -14 for Fisher-344 rats. We have demonstrated that the binding of chloroform to hemoglobin appears to have the following attributes of a dose monitor: (1) easily accessible from laboratory animals (and humans); (2) dose dependent; (3) stability, so that exposure can be determined weeks after it has ceased; (4) integration of low exposures which individually would be undetectable. (Author abstract) (15 Refs)

49. METABOLISM AND ACTIVATION OF AFLATOXIN B1 BY RECONSTITUTED CYTOCHROME P-450 SYSTEM OF RAT LIVER.

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Cancer Res; 42(3):1120-1124 1982

Metabolism and activation of aflatoxin B1, a potent hepatocarcinogenic and mutagenic mycotoxin of Aspergillus flavus, were investigated in the reconstituted enzyme system composed of purified NADPH-cytochrome P-450 reductase and cytochrome P-450 or P-448 or rat liver. The aflatoxin M1 formation was strictly mediated by P-448 purified from the liver microsomes of polychlorobiphenyl- and 3-methylcholanthrene-treated rats, while the aflatoxin Q1 formation, as well as the binding to DNA, were catalyzed by both P-450 and P-448. Differences between the kinetic data on metabolism and activation of aflatoxin B1 obtained with the reconstituted cytochrome systems and those obtained with the microsomal and nuclear systems were discussed, and the significance of these biochemical data in the in vivo carcinogenicity of aflatoxin B1 was evaluated. (Author abstract) (37 Refs)

50. METABOLISM OF N-NITROSAMINES BY CULTURED HUMAN AND RAT ESOPHAGUS.

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Cancer Res; 42(4):1307-1311 1982

The metabolism of several N-nitrosamines (N-nitrosodimethylamine, N-nitrosoethylmethylamine, N-nitrosodiethylamine, N-nitrosobenzylmethylamine, and N-nitrosopyrrolidine) in cultured human and rat esophagus has been investigated by measuring CO2, metabolites with an oxo group and metabolites bound to DNA. Both acyclic and cyclic N-nitrosoamines were metabolized by rat esophagus. The highest level of metabolite binding was seen with N-nitrosobenzylmethylamine, an organotropic carcinogen for the rat esophagus. The binding level was about 100-fold higher than in human esophagus. This compound methylated rat esophageal DNA at positions 7 and O6 of guanine. The level of benzylation in rat was one-tenth the level of methylation. Formation of benzaldehyde exceeded that of formaldehyde plus CO2 by a factor of 6, indicating that the methylene group was preferentially oxidized. N-Nitrosoethylmethylamine was preferentially oxidized by rat esophagus in the ethyl group. The highest binding level to DNA from this compound was observed with the methyl group. No binding was detected to human esophagus. N-Nitrosopyrolidine was oxidized by both rat and human esophagus in the alpha position, as measured by the formation of 2,4-dinitrophenylhydrazone derivative of 4-hydroxybutanal. Binding of metabolites of N-nitrosopyrrolidine to DNA was detected only in rat esophagus. As measured by the formation of both CO2 and formaldehyde, N-nitrosodimethylamine was metabolized by both human and rat esophagus. While most of the radioactivity associated with DNA was found to be incorporated into guanine and adenine, methylation of the guanine positions 7 and O6 was detected by chromatography of the hydrolyzed rat DNA. The results indi-

cate significant quantitative and perhaps qualitative differences between cultured rat and human esophagus in their ability to activate N-nitrosamines, although unknown physiological differences after culture may contribute to this difference. (44 Refs)

51. A FREE RADICAL MECHANISM FOR ARYLAMINE INDUCED CARCINOGENESIS INVOLVING PEROXIDES.

Vasdev S, Tsuruta Y, O'Brien PJ
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Biochem Pharmacol; 31(4):607-608 1982

A 1 e oxidation of N-methyl-4-aminoazobenzene (MAB) catalyzes more binding than the 2 e monooxygenase mechanism in the presence of liver sulfotransferase. Covalent binding of (14C)MAB metabolites to exogenous DNA or microsomal protein demonstrated that hydroperoxide was almost 400x more effective than NADPH in catalyzing the binding. NADPH/reductase may reduce the radical formed by the 1 e oxidation pathway of cytochrome P450. The hydroperoxide catalyzed binding was not affected by addition of cytosol, while the NADPH system was markedly enhanced. Addition of ATP and sulfate further enhanced the cytosol effect, suggesting that the cytosol effect was probably due to sulfotransferase acting on the NOH MAB formed by the 2 e oxidation pathway carried out by microsomal amine oxidase/4. No NOH MAB was formed with hydroperoxide. Cytochrome P450 catalyzed both N demethylation and ring hydroxylation of MAB and the N hydroxylation was catalyzed by microsomal amine oxidase. In dogs and mice, the 1 e pathway of the monooxygenase activity of bladder and lung tissue may be responsible for carcinogenesis in these organs following administration of p-dimethylaminoazobenzene. In mouse liver carcinogenesis, both the 1 e and 2 e pathways should be considered. (9 Refs)

EFFECT OF CARCINOGENS ON MACROMOLECULAR SYNTHESES

52. NEOPLASTIC TRANSFORMATION OF SYRIAN HAMSTER EMBRYO CELLS BY BISULFITE IS ACCOMPANIED WITH A DECREASE IN THE NUMBER OF FUNCTIONING REPLICONS.

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Carcinogenesis; 3(1):27-32 1982

Bisulfite, a chemical that at neutral pH does not induce mutations at two loci in Chinese hamster V-79 cells, induces transformation of Syrian hamster embryo cells. Although bisulfite affects DNA metabolism, there was no evidence of bisulfite-induced DNA damage. Bisulfite induced no excision repair replication, caused no DNA strand breaks detectable in alkaline sucrose gradients, had no effect on the size distribution of DNA nascent daughter strands, and did not affect excision on post-replication repair of uv-induced damage. However, bisulfite did induce a dose-dependent decrease in the rate of DNA replication pe r cell, apparently due to a reduction in the number of functioning replicons. Since the data indicate that bisulfite causes no detectable DNA damage, it appears that bisulfite induces transformation by a non-mutagenic event that could involve the inhibition of semi-conservative DNA synthesis. (Author abstract) (27 Refs)

53. CHANGES OF CHROMATIN STRUCTURE IN THYMOCYTES OF IRRADIATED RATS. IMMUNOCHEMICAL ANALYSIS.

Ermekova VM, Melkonian OS, Nazarova LF, Nanazashvili MG, Umanskii SR
Inst. Biological Physics, Pushchino, USSR
Radiobiologiia; 21(6):813-817 1981

To evaluate the mechanisms of DNA degradation in irradiated thymocytes, rats were irradiated with 1,000 rads, and chromatin and total nonhistone proteins (TNHP) were isolated from thymocytes. In another series of experiments, isolated chromatin was irradiated in vitro at 4,730 rads/min. Chromatin and TNHP were mixed with equal volume of complete Freund adjuvant and used for immunization of the rabbits. Immunochemical analysis showed that immune sera and isolated IgG formed specific complexes with chromatin. IgG isolated from the sera of nonimmunized rabbits did not react with chromatin. The products of chromatin degradation were significantly more active in reaction of complement fixation (RCF) than the control chromatin. In vitro irradiation of chromatin with 1,000 rads did not affect its reactivity in RCF; significant increase of the accessibility of antigenic determinants was detected only after irradiation with 20,000-50,000 rads. (8 Refs) (In RUS)

54. THE SENSITIVITY OF ACTIVE AND INACTIVE CHROMATIN TO IONIZING RADIATION-INDUCED DNA STRAND BREAKAGE.

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Div. Radiation Biology, Dept. Radiology, Case Western Reserve Univ., Cleveland, OH, 44106
Int J Radiat Biol; 41(1):71-77 1982

Sensitivity of Tetrahymena pyriformis strain GL-C DNA in actively transcribing and inactive states was compared with regard to gamma-radiation-induced single-strand break (SSB) induction. Following electrophoresis on agar gels and hybridization with poly(A)RNA, nuclear DNA from irradiated cells was found in broader peaks and contained smaller fragments than did control DNA. In unirradiated cells, the profiles of transcribing and bulk DNA were similar, suggesting that transcribing genes are initially randomly distributed in all fragment sizes of nuclear DNA. Transcribing DNA from irradiated cells was found preferentially among the smaller fragments of total DNA. The apparent difference in the behavior of transcribing DNA from unirradiated and irradiated cells was not due to contamination of poly(A)RNA with ribosomal RNA. The av mol wt of transcribing DNA was slightly but consistently greater than that of total nuclear DNA in unirradiated cells, while the reverse was true for irradiated DNA. When unirradiated nuclear DNA was mechanically sheared into fragment sizes comparable to those from irradiated cells, the similarity of the profiles of chromosomal and transcribing DNA was maintained after reduction of the fragment size of nuclear DNA. In vitro, no differences in the radiation sensitivities of transcribing and chromosomal DNA were observed. Kinetics of SSB rejoining are described. The results indicated that chromatin organization is important in the determination of the sensitivity of cellular DNA towards gamma-radiation. Not only yield but also the rate of repair of SSB is greater in actively transcribing genes than in the total nuclear DNA. (30 Refs)

55. CHANGES IN THE SUPERCOILED STRUCTURE OF NUCLEAR DNA IN RAT AND HUMAN PERIPHERAL BLOOD LYMPHOCYTES AFTER GAMMA-IRRADIATION.

Klimov NA, Vashchenko VI, Kolyubaeva SN, Komar VE
Central Res. Inst. Roentgenology and Radiology, USSR Ministry Public Health, Leningrad 188646, USSR
Int J Radiat Biol; 41(2):221-225 1982

Damage and repair of DNA as indicated by changes in the supercoiled structure (SCS) of DNA were studied in vitro and in vivo. After exposure to gamma-irradiation DNA showed a relaxation of SCS. Both in vitro and in vivo DNA was repaired in a three-phase process reflecting repair of single-strand breaks, degradation of DNA, and further repair of single-strand breaks. The process was delayed in vivo, suggesting the presence of inhibiting factors. (21 Refs)

56. THE EFFECT OF IONIZING RADIATION ON PRODUCTION OF HETEROKARYONS AND THE INTERACTION OF THEIR NUCLEI.

Hofmanova J, Spurna V
Inst. Biophysics, Czechoslovak Acad. Sciences, Kralovopolska 135, CS-612 Brno 65, Czechoslovakia
Stud Biophys; 86(3):203-204 1981

Irradiated L cells (500-5,000 rads) were incubated with non-irradiated mouse lymphosarcoma LS/BL cells. Within different time periods after the fusion, the formation of heterokaryons and DNA synthesis in the irradiated cells were determined. The incidence of heterokaryons after the fusion with irradiated L cells was 2x greater than that after the fusion with nonirradiated L cells. The rate of DNA synthesis in the irradiated L cells was significantly lower than that in nonirradiated L cells. (2 Refs)

57. ACUTE EFFECTS OF SELECTED HEPATOTOXIC AGENTS ON POLYRIBOSOMES AND PROTEIN SYNTHESIS IN THE LIVERS OF RATS FED PURIFIED DIETS CONTAINING HEPATOCARCINOGENS.

Sidransky H, Verney E
Dept. Pathology, George Washington Univ. Medical Center, Washington, DC, 20037
Exp Mol Pathol; 36(1):72-85 1982

This investigation was concerned with the effects of certain hepatocarcinogens ingested for long- or short-term intervals upon selected responses of rat liver to specific hepatotoxic stimuli. Rats fed ad libitum for long (3 to 45 wk) periods or force-fed for short (3 days) periods purified diets containing a single hepatocarcinogen, ethionine, N-2-fluorenylacetamide, 3'-methyl-4-dimethylaminoazobenzene, or thioacetamide, were subjected to the acute administration of a single hepatotoxic agent, such as puromycin, actinomycin D, sparsomycin, hypertonic NaCl or CCl4, and hepatic protein synthesis (in vitro) and polyribosomal aggregation were evaluated. Relating to in vitro protein synthesis, in long-term experiments, puromycin induced less inhibition in the experimental groups than in the control (basal diet) group; and actinomycin D inhibited all groups similarly; while in the short-term experiments, puromycin induced less inhibition in the experimental groups than in the control group; actinomycin D inhibited the basal and ethionine groups more than the other groups; sparsomycin induced variable degrees of inhibition, with the ethionine group showing the most and the N-2-fluorenylacetamide and thioacetamide groups showing the least; hypertonic NaCl markedly inhibited all groups similarly; and CCl4 induced somewhat variable degrees of inhibition, with the thioacetamide group showing less than the other groups. In a few long-term experiments where hepatomas were evaluated in relation to surrounding liver tissue, puromycin administration induced less inhibition in the hepatomas than in the surrounding liver while actinomycin D administration induced similar inhibition in both groups. In general, in all experiments the degree of polyribosomal disaggregation was parallel to that of inhibition of protein synthesis (in vitro). The results reveal that the livers of rats fed purified diets containing selected hepatocarcinogens responsed in a variable manner in regard to protein synthesis (in vitro) and status of polyribosomal aggregation to the acute administration of selected hepatotoxic agents. (Author abstract) (23 Refs)

58. MEMBRANE-BOUND SIALOGLYCOPROTEINS FROM RAT LIVER AFTER COMBINED EXPOSURE TO BENZO(A)PYRENE AND SULFUR DIOXIDE.

Merkur'eva RV, Bushinskaia LI, Skvortsova NN, Dolinskaia SI, Shaternikova IS, Nozdracheva LI
Lab. Biochemistry and Hygiene of Atmospheric Pollutants, A. N. Sysin Inst. General and Community Hygiene, Moscow, USSR
Vopr Med Khim; 27(6):791-794 1981

The effect of carcinogens on metabolism of membrane-bound sialoglycoproteins (MBSGP) was studied in random-bred albino male rats. Animals were exposed to benzo(a)pyrene (BP) in combination with sulfur dioxide (SD). Within 2 wk, 6 wk, and 6 mo after exposure, rats were sacrificed and the distribution of MBSGP in the liver was determined. Combined exposure to BP and SD resulted in the increase of N-acetylneuraminic acid content in liver mitochondria and liver lysosomes, decrease of neuraminidase activity, and increase of beta-galactosidase activity. Carcinogens did not affect lipid peroxidation in the liver tissue. (20 Refs) (In RUS)

59. REGULATION OF GAMMA-GLUTAMYLTRANSPEPTIDASE IN RAT HEPATOCYTE MONOLAYER CULTURES.

Edwards AM
Clinical Biochemistry, Sch. Medicine, Flinders Univ. South Australia, Bedford Park, South Australia 5042, Australia
Cancer Res; 42(3):1107-1115 1982

Hepatocytes isolated as a relatively pure population from normal adult rats were maintained in primary monolayer culture for 4 to 7 days on plastic dishes. Factors affecting activity of gamma-glutamyltranspeptidase (GGT) in culture were investigated to establish a basis for in vitro studies on carcinogen-induced changes in GGT. Freshly plated cultures contained few GGT-positve cells (0.4%) and very low total GGT activity, but with all media tested, activity increased progressively with time in culture, the extent of increase depending on medium composition. For hepatocytes in modified Waymouth medium alone (control cultures), there was a slow rise in activity after a 1-to 2-day lag period. This increase was enhanced up to 10-fold in the presence of 3 uM dexamethasone for cells on plastic but only 2-to 3-fold for cells on collagen gels. The time- and dose-dependent action of dexamethasone was prevented by cycloheximide, partly blocked by actinomycin D, and reversed after several hr by removing the steroid, when GGT activity decreased with a max half-life of 60 to 80 hr. These observations suggest that dexamethasone caused reversible enzyme induction dependent on continuing RNA and protein synthesis. Cell maintenance with fetal calf serum or with N6,mO21-dibutyryl adenosine 3':5'-monophosphate or gluca-

gon markedly reduced the extent of induction by dexamethasone and slightly lowered activity in control cultures. Maintenance at lower pH within the range of 7.2 to 7.8 or at higher glucose concentrations within the range of 2.8 to 28 mM also resulted in markedly lower GGT activities in control or dexamethasone-induced cultures. Glucose repression was independent of insulin concentration. The reversible induction and repression of GGT may reflect broad changes in hepatocyte gene expression rather than specific controls of GGT function. Since GGT in cultured hepatocytes is subjected to regulation by a variety of noncarcinogens, caution is required in its use as a preneoplastic marker. Nevertheless, the identification of culture media which preserve low activity may allow studies on carcinogen-induced changes in GGT as a probe of the early events in vitro hepatocarcinogenesis. (Author abstract) (62 Refs)

REVIEWS

60. XERODERMA PIGMENTOSUM VARIANTS.

Cleaver JE, Coriell LL, Mulivor RA
(c/o Greene), Inst. Medical Res., Copewood St., Camden, NJ, 08103
Cytogenet Cell Genet; 31(3):188-192 1981

Xeroderma pigmentosum (XP) consists of the subgroups A, B, C, D, E, F, G, and variant. The first seven subgroups have a defect in the mechanisms of excision repair of DNA damage by UV radiation. The XP variant subgroup has normal excision repair but abnormal replication of UV-damaged DNA. The defect may be the loss of a gene product required for replication past damaged sites. Cultures of XP variant cells from a variety of ethnic groups and geographical areas are available and should be useful for investigating actinic carcinogenesis in XP. (26 Refs)

61. EFFECT OF POLYAMINES ON ENZYMES INVOLVED IN DNA REPAIR.

Kleppe K, Osland A, Fosse V, Male R, Lossius I, Helland D, Lillehaug JR, Rane AJ, Kleppe RK, Nes IF
Dept. Biochemistry, Univ. Bergen, Bergen, Norway
Med Biol; 59(5/6):374-380 1981

The effects of polyamines on UV incision nuclease, DNA polymerase I, DNA ligase and polynucleotide kinase, apurinic- or apyrimidinic (AP)- endonucleases, and enzymes involved in folding and unfolding of chromosomes are reviewed. Polyamine-induced cleavage of AP-sites is also discussed. Spermine and spermidine have been found to be more efficient in causing hydrolysis of DNA than cadaverine or putrescine. (29 Refs)

62. MOLECULAR MECHANISM OF ADAPTATION OF CELLS TO LOW LEVELS OF CARCINOGENIC AGENTS.

Villani G
Laboratoire de Pharmacologie et de Toxicologie Fondamentales, CNRS, 205, route de Narbonne, 31078 Toulouse Cedex, France
Pathol Biol (Paris); 30(2):117-123 1982

Adaptation of Escherichia coli, rat liver cells and human fibroblasts to the cytotoxic and mutagenic effects of alkylating agents such as N-methyl-N'-nitro-N-nitrosoguanidine (MMNG), dimethylnitrosamine (DMN), and N-methylnitrosourea (MNUA) are reviewed. Through exposure to low doses of alkylating agents an increased numbers of cells are able to survive the challenge of high doses; fewer mutations are observed among survivors. Adaptation in E coli, a process involving DNA repair, is inducible and non-specific, consisting of two dissociable phenomenon (increased survival, decreased mutagenesis) controlled by gene polA, and is independent of other repair systems. Studies of adaptation to MNNG in E coli have shown that following adaptation, the methyl group is transferred from the O-6 position of guanine to an acceptor protein which is rapidly inactivated. After exposure to a challenge dose of DMN, fewer DNA O-6 methylguanine lesions were found in livers of rats preexposed to low doses of DMN for 4-6 wk as compared with untreated controls; the same number of N-7 methylguanine and N-3 methyladenine lesions were found in both groups. Pretreatment of cultured human fibroblasts with low doses of MNNG or MNNU increased their resistance to challenge; fewer sister chromatid exchanges were observed following the challenge. (41 Refs) (In FRE)

63. PROCANCER CLASS OF GENES AND GENERATION OF CHROMOSOME MUTATION.

Sasaki MS, Ejima Y
Radiation Biology Center, Kyoto Univ., Yoshida-konocho, Sakyo-ku, Kyoto 606, Japan
Gann Monogr Cancer Res; 27:85-94 1982

The nature of inherent mutation associated with chromosome instability and high cancer risks is discussed. Human genetic syndromes associated with chromosome instability include Fanconi's anemia (FA), ataxia telangiectasia (AT), Bloom's syndrome (BS), incontinentia pigmenti (IP), and, perhaps xeroderma pigmentosum (XP). Chromosome aberrations are primarily of the chromatid type, indicating that the chromosome mutations in these diseases arise in connection with DNA replication. FA, AT, and IP have a significantly high frequency of chromosome aberrations, while the other diseases show normal aberration rates. DNA damage left unrepaired in AT and FA cells might not be subject to repair by post-replication error-prone repair mechanisms or such a mechanism might not operate in these cells. Genetically-determined cancer proneness appears to be caused by an intrinsic sensitivity of instability to chromosome mutation; gross chromosomal change is a prime importance in mutation toward cancer. Certain types of procancer genes with dominant traits express a mutator function and promote chromosome recombination in their somatic cells. Such mutations of de novo origin occur in familial polyposis coli, Gardner's syndrome, Peutz-Jegher's syndrome, nevoid basal cell carcinoid syndrome, hereditary retinoblastoma, dominantly-inherited familial leukemia, and familial colon cancer. The nature of germinal mutations responsible for organ-specific cancer proneness is discussed. (37 Refs)

64. GENETIC ASPECTS OF DNA REPAIR DEFICIENCY.

Takebe H, Ishizaki K, Yagi T
Radiation Biology Center, Kyoto Univ., Yoshida-konocho, Sakyo-ku, Kyoto 606, Japan
Gann Monogr Cancer Res; 27:13-19 1982

DNA repair in human cells, specifically those of persons with xeroderma pigmentosum (XP), is reviewed. A survey of the relative levels of unscheduled DNA synthesis (UDS) in XP patients in Japan revealed a unique XP group, group F, in which patients have mild symptoms despite their apparently low repair capacities. In this group, UDS may not represent the actual capacity for excision repair; the resynthesis step was slower than in normal cells and UDS measured during the first few hr after UV irradiation detected only a small portion of the total repair. Inactivation of colony-forming ability and UDS did not correspond in Bloom's syndrome cells treated

with mitomycin C and XP strains did not demonstrate high sensitivity to antipain. The presence of UDS suggests the presence of DNA damage subject to some type of repair, but is not proof. The frequency of the population at genetically high risk of cancer in Japan is reported for XP, ataxia telangiectasia, Bloom's syndrome, Fanconi's anemia, retinoblastoma, familial polyposis coli, and Down's syndrome. Overall, the frequency of the population with a high risk of cancer may be 3%. The genetic fa ctor should not be considered a major cause of cancer in Japan. (16 Refs)

65. THE USE OF MAMMALIAN CELL MUTANTS TO STUDY THE MECHANISMS OF CARCINOGENESIS.

Trosko JE, Chang CC, Warren ST, Lin PK, Wade MH, Tsushimoto G
Dept. Pediatrics and Human Development, Michigan State Univ., Coll. Human Medicine, East Lansing, MI, 48824
Gann Monogr Cancer Res; 27:159-179 1982

Use of mammalian cell mutants to study the mechanisms of carcinogenesis is reviewed. A genetic approach was used to study molecular mechanisms of initiation and promotion. It was shown that different mutagens induce different types of mutations and that phenotypic expression is influenced by tumor promoters or antipromoters, while mutation fixation is not. General considerations of in vitro mutagenesis at the gene level are discussed. Study of mutagen-sensitive DNA-repair deficient mutants and xeroderma pigmentosum and Bloom's syndrome cells demonstrated that a defect in DNA repair or DNA replication may cause mutagenesis. An in vitro assay to detect tumor promoters was designed with the basic premise that all tumor promoters block metabolic cooperation. Inhibition of cell-cell communication by known tumor promoters might be one of the initial events triggered by tumor promoters. It is possible to study the mechanism of tumor promoters and to screen for environmental promoters. An hypothesis for the relationship of metabolic cooperation and carcinogenesis is proposed. (144 Refs)

66. EXCISION REPAIR OF DNA DAMAGE PRODUCED BY 4-NITROQUINOLINE 1-OXIDE IN CULTURED MAMMALIAN CELLS: ITS RELATION TO CARCINOGENESIS.

Ikenaga M
Dept. Fundamental Radiology, Osaka Univ. Faculty Medicine, Nakanoshima 4-3-57, Kita-ku, Osaka 530, Japan
Gann Monogr Cancer Res; 27:21-32 1982

Molecular mechanisms of repair of DNA lesions induced by 4-nitroquinoline 1-oxide (4NQO) in cultured mammalian cells were studied. In UV-irradiated xeroderma pigmentosum (XP) cells, the level of 4NQO-induced unscheduled DNA synthesis (UDS) was lowest in complementation group A, and increased in groups B, C, D, and E in order. In Cockayne's syndrome cells, normal levels of UDS after UV or 4NQO treatment were found. Epidermodysplasia verruciformis cells showed a slightly reduced level of UDS after UV irradiation and were highly sensitive to 4NQO. Variable responses to 4NQO were observed in cells of ataxia telangiectasia. The major 4NQO lesions produced in DNA of cultured human cells were a stable major 4NQO-guanine adduct, a stable minor 4NQO-guanine adduct, a stable major 4NQO-adenine adduct, and an unstable major 4NQO-guanidine adduct that releases 4-aminoquinoline 1-oxide upon hydrolysis. The excision repair of 4NQO-purine adducts from DNA of normal human cells and its absence in XP cells was demonstrated. Studies with mouse cells demonstrated that 4NQO-purine adducts are the major cause of 4NQO carcinogenesis. These findings are discussed with respect to excision repair, which may be important in chemical carcinogenesis. (49 Refs)

67. DNA REPAIR AND MUTAGENESIS OF SINGLE-STRANDED BACTERIOPHAGES.

Doubleday OP, Brandesburger A, Godson GN, Wagner R, Radman M
Rue des Chevaux 67, B-1640 Rhode-St-Genese, Belgium
Gann Monogr Cancer Res; 27:3-11 1982

DNA sequences of revertants of two M13 amber mutants, am6H2 and am7H3, isolated from populations of irradiated and unirradiated phages grown in irradiated or unirradiated host bacteria were analyzed. DNA sequences in the region of the amber mutation were determined. Forty-nine revertants of am6H1 and 125 of am7H3 were sequenced. All detectable single nucleotide changes were seen except the thymine-adenine-guanine (TAG) to GAG change, which was not found for either amber. No obvious specificity of mutagenesis by either UV- or gamma-irradiation of target DNA were seen. No specificity of mutagenesis by an error-prone repair activity (SOS repair system) acting upon either irradiated or unirradiated DNA was revealed, although induction of host SOS repair activity increased revertant yields. Both transitions and transversions, and changes involving each of the three bases of the amber codon were induced by all combinations of host cell and target irradiation. No pattern of revertant sequences was obtained to suggest that pyrimidine dimers are the primary sites of base changes. DNA sequences of revertants isolated from UV-irradiated phage populations demonstrated that pyrimidine dimers are not the main sites of mutations in UV-irradiated DNA. UV-induced mutagenesis may be untargeted or may occur at sites of lesions other than pyrimidine dimers. (23 Refs)

68. SISTER CHROMATID EXCHANGES AND MUTAGENIC CARCINOGENS.

Wolff S
Lab. Radiobiology, Univ. California, San Francisco, CA, 94143
Gann Monogr Cancer Res; 27:109-124 1982

Use of sister chromatid exchange (SCE) induction for detecting mutagenic effects in mammalian cells is reported. SCEs are produced with unrepaired lesions are present when the cell passed through S phase and chromosome replicated. Some chemical mutagens caused a 10-fold increase in background level of SCEs at concentrations of the chemical less than 1/100th of that required to induce ordinary chromosomal aberrations. Cultured Chinese hamster ovary cells with rat liver microsomes can be used to detect SCE induction. Suspected mutagens can be prescreened with the SCE test in sensitive mammalian cells by treating the cells in vitro with and without S-9 mix. Negative compounds should be tested in an in vivo test system to determine if the compounds can be activated under in vivo conditions. The SCE test was used to determine the following: which benzene metabolites were most likely responsible for the biologic effects, the stage of embryogenesis at which cells that are genetically capable of producing aryl hydrocarbon hydroxylase activated promutagens or procarcinogens, how long lesions induced by a short-lived proximate carcinogen last in cells of differing repair capacity, and whether mammalian cells exhibit novel DNA repair mechanisms. (58 Refs)

69. EXCISION AND CROSSLINK REPAIR OF DNA AND SISTER CHROMATID EXCHANGES IN CULTURED HUMAN FIBROBLASTS WITH DIFFERENT REPAIR CAPACITIES.

Fujiwara Y, Kano Y, Paul P, Goto K, Yamamoto K, Miyazaki N
Dept. Radiation Biophysics, Kobe Univ. Sch. Medicine, Kusunoki-cho 7-5-1, Chuo-ku, Kobe 650, Japan
Gann Monogr Cancer Res; 27:33-44 1982

The relationship between sister chromatid exchange (SCE) induction and DNA repair was studied by evaluating the role of UV excision repair. The roles of interstrand crosslinking and repair in the induction of SCE in fibroblasts of xeroderma pigmentosum (XP) complementation groups (A to G and a variant group), Cockayne's syndrome (CS), and Fanconi's anemia (FA) with different repair capacities and predispositions to malignancies were studied. Killing sensitivities of the three types of cells to UV, 4-nitroquinoline-1-oxide (4NQO), and monofunctional decarbamoyl mitomycin C (DCMC) are reported. The XP groups were deficient in the initial steps of dimer excision repair in the order of A = G greater than C greater than D greater than D = F greater than variant. The extent of dimer-repair deficiency strictly determined the killing sensitivity of XP cells. Studies of the susceptibilities of XP and CS cells to SCEs induced by mutagens demonstrated that in the most defective XP group-A cells, the SCE induction rate by UV, 4NQO, and DCMC was a 3-5-fold higher than in normal cells. FA cells were approx 1.7x more sensitive to SCE induction by MC than normal cells and the SCE rate induced by DCMC was the same as that of normal cells. In XP cells, a six-fold higher SCE rate was observed after DCMC, and only a slightly higher SCE rate was observed after MC. Thus, part of cross-link damage may yield SCE. Caffeine synergistically increased UV-induced SCEs, but not UV-induced mutations in V79 cells, thus, dissociated SCE from mutation. (21 Refs)

70. THE INDUCTION OF MUTATION AND CELL DIFFERENTIATION BY CHEMICALS WHICH INITIATE OR PROMOTE TUMOR FORMATION.

Huberman E
Div. Biological and Medical Res., Argonne Natl. Lab., Argonne, IL, 60439
Gann Monogr Cancer Res; 27:127-144 1982

Detection of tumor promoting chemicals in mammalian cell culture systems is described. Chemical carcinogens are mutagenic for mammalian cells, with their degree of mutagenicity correlating with their degree of carcinogenicity. In some cases, the metabolites responsible for mutagenesis are also responsible for initiating the carcinogenic event. A cell/organ type specificity can be established with a cell-mediated assay. The effect of tumor promoters such as the phorbol-diesters in cultured human HO melanoma and human HL-60 promyelocytic leukemia cells was studied. In both HO and HL-60 cells, the ability of ten different phorbol esters to induce differentiation correlated with their tumor-promoting activity in mouse skin. Changes in polyamine levels may involve biological pathways other than the known biosynthetic ones and these pathways or their by-products may be involved in the control of cell growth and differentiation in HL-60 cells. Studies of specific binding of 20-[3H]-phorbol 12,13-dibutyrate (PDBu) in HL-60 cells demonstrated that down regulation of specific PDBu binding is an important phenomenon involved in the mechanism of action of phorbol esters and may lead to modification of various biological and biochemical events involved in cellular differentiation and perhaps tumor promotion. Human HO melanoma and HL-60 leukemia cells may be useful for studying the mode of action of known tumor promoters and in the identification of some unknown classes of tumor-promoting agents. (82 Refs)

71. THE DETECTION OF GENOTOXIC CHEMICALS IN THE HEPATOCYTE PRIMARY CULTURE/DNA REPAIR TEST.

Williams GM
American Health Foundation, Naylor Dana Inst. for Disease Prevention, Valhalla, NY, 10595
Gann Monogr Cancer Res; 27:45-55 1982

Use of the hepatocyte primary culture (HPC)/DNA repair test for detection of genotoxic chemicals is reported. Hepatocytes obtained from livers of rats, mice, hamsters, or rabbits are cultured on plastic coverslips and exposed to the test chemical for 5-18 hr with 3H-thymidine. Cells are then fixed and processed for emulsion autoradiography. Of 73 compounds tested, 96% of known carcinogens were positive, 8 chemicals of unknown carcinogenicity were positive and 2 were negative, and all 13 noncarcinogens were negative. The test can be used to examine species differences in xenobiotic biotransformation and DNA repair response in a specific, well characterized cell type. Since liver cells do not respond to chemicals requiring bacterial metabolism, supplementation with the specific bacterial enzyme suspected of being involved in the biotransformation of the test chemical may be useful. All hepatocarcinogenic drugs and organochlorine pesticides were negative in the HPC/DNA repair test, supporting the concept that these carcinogens operated by epigenetic mechanisms, which in some cases appear to be promoting effects. Us of this test with other in vitro short-term tests may be useful for classifying carcinogens as epigenetic. (39 Refs)

72. ONCOGENES.

Bishop JM
Univ. California, San Francisco, CA
Sci Am; 246(3):80-84,87-92,154 1982

Recent developments in cancer research concerning inducement of cancerous growth are reviewed. Some tumor viruses (TV) are oncogenic only in animals that are not hosts in nature, others are oncogenic only in their natural host. Transformation of cultured cells by TV makes possible the examination of the interaction of a TV with a host cell under controlled conditions, thus avoiding the difficulties associated with experiments in animals. Some viruses have a single gene which can induce tumors, or in some cases, a few such 'oncogenes'. Retroviruses (RV) are the only TV with an RNA genome. The src oncogene of Rous sarcoma virus is discussed. The protein encoded by src is a 60,000 mol wt phosphoprotein. Phosphorylation of tyrosine is a common characteristic of oncogene-encoded enzymes and also has a role in regulating the growth of normal cells. The mutational hypothesis proposes that viral oncogenes differ from their cellular progenitors as a result of mutations introduced when the cellular genes were copied into the RV genome. The dosage hypothesis suggests that RV oncogenes overburden cells with too much essentially normal proteins carrying out normal functions. Excessive activity might tip the balance of regulation toward incessant growth. In tumors induced by the chicken lymphoma viruses, the viral DNA is almost always inserted into cellular DNA in the immediate vicinity of a single cellular oncogene, and the expression of the cellular oncogene is greatly amplified. Gene-length bits of DNA isolated from some tumors can transmit the property of cancerous growth when they are introduced into previously normal cells in culture. (4 Refs)

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BIOLOGICAL ASPECTS OF DNA ALTERATION AND REPAIR IN RELATION TO CARCINOGENICITY

1. COMPLEMENTATION OF THE DEFECTS IN DNA SYNTHESIS IN IRRADIATED AND UNIRRADIATED ATAXIA-TELANGIECTASIA CELLS.

Murnane JP, Painter RB

Lab. Radiology and Environmental Health, Univ. California, San Francisco, CA, 94143

Proc Natl Acad Sci USA; 79(6,part1):1960-1963 1982

Mutant subtypes in the human genetic disease ataxia-telangiectasia (A-T) were classified by means of an assay system that monitors complementation of defects in DNA synthesis. Anomalies in DNA synthesis have been observed previously in A-T cells, both in their failure to inhibit DNA synthesis immediately after exposure to ionizing radiation and in their prolonged S phase. Polyethylene glycol-mediated cell fusion and autoradiography were combined with selective identification of different A-T cell populations by fluorescent colored microspheres to determine complementation capabilities of various A-T cell combinations. Five complementation groups were identified by both a 30-40% increase in the rate of DNA synthesis in unirradiated heterokaryons and the appearance of normal inhibition of DNA synthesis after x-irradiation of heterokaryons. The correlation observed between these phenomena suggests that the defects in A-T cells involve problems in initiation of DNA synthesis. (Author abstract) (20 Refs)

2. ABNORMAL LEVELS OF UV-INDUCED UNSCHEDULED DNA SYNTHESIS IN ATAXIA TELANGIECTASIA CELLS AFTER EXPOSURE TO IONIZING RADIATION.

Jaspers NG, Bootsma D

Lab. Cell Biology and Genetics, Erasmus Univ. Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands

Mutat Res; 92(1/2):439-446 1982

The baseline levels of UV-induced unscheduled DNA synthesis (UDS) in normal human fibroblast cell lines (C3RO and C5R0) and ataxia-telangiectasia (AT) fibroblast cell lines (AT5BI, AT4BI, AT2BE, AT1PWA, and AT3BI) were determined to be the same. Exposure to x-rays (XR: up to 20,000 rads) significantly altered UV-induced UDs in the AT cells but not in the normal cells. In AT cell lines showing a reduced capacity for gamma-ray-induced repair DNA synthesis (excision-deficient AT cell lines AT3BI and AT2BE), XR exposure inhibited UV-induced UDS. In AT cell lines showing a normal capacity for gamma-ray-induced repair DNA synthesis (excision-proficient AT cell lines), XR exposure stimulated UV-induced UDS. The excision-deficient and excision-proficient AT cell lines showed different dose-response relationships for both UV and XR. The two types of AT cells may have different molecular defects. Altered levels of repair DNA synthesis after UV exposure in AT cells may be secondary consequences of the way the cells handle DNA damage induced by ionizing radiation. (14 Refs)

3. X-RAY, UV AND CHEMICAL MUTAGEN SENSITIVITIES OF SKIN FIBROBLASTS FROM PATIENTS WITH FAMILIAL AND CHROMOSOME 13Q-RETINOBLASTOMAS.

Fujiwara Y, Miyazaki N, Kano Y, Takahashi T, Kaneko A

Dept. Radiation Biophysics, Kobe Univ. Sch. Medicine, Kusunoki-cho 7-5-1, Chuo-ku, Kobe 650, Japan

J Radiat Res (Tokyo); 22(4):472-476 1981

The sensitivities of human retinoblastoma (RB) fibroblast strains (AGG1142, RB1JTO, RB1KO) and reference strains NHSF6, NHSF46, and NHSF63 to killing by 170 kVp x-rays, 254 nanometer (nm) UV light, methyl methanesulfonate (mms), monofunctional decarbamoyl mitomycin C (DMC), and bifunctional mitomycin C were tested. The RB strains displayed radiation and mutagen survival curves that were in general similar, and fell within the normal range, as measured by the response of the three NHSF strains. These results strongly suggest that AG1142 cells can repair various types of DNA damage induced by the radiation and cross-linking agents. A 3 to 4-fold increase in sensitivity of RB1JTO (13q-) and RB1KO cells to MMS killing, and a 2-fold higher susceptibility of RB1JTO cells to a UV-type agent (DMC), but not to 254 nm UV was observed, suggesting that MMS and DMC sensitivities may not be universal throughout the RB strains studied. The hypothesis that a specific region on 13q14 may be associated with a presumptive x-ray repair locus governing x-ray sensitivity in an intimate relation to the incidence of RB and second tumors is not supported. (15 Refs)

4. A CHILD WITH XERODERMA PIGMENTOSUM AND G6PD DEFICIENCY.

Harper JI, Copeman PW

Page Street Wing, Westminister Hosp., Page St., London SW1P, England

Clin Exp Dermatol; 7(2):213-216 1982

A 2-yr-old male, sun-sensitive for over 1 yr, and having several relatives with xeroderma pigmentosum (XDP), was tested for DNA repair synthesis in UV-irradiated fibroblasts, and for glucose-6-phosphate dehydrogenase (G6PD). The G6PD assayed at 10% of the normal lower limit. The DNA repair was only 14% of expected. The subject's XDP classification was XP-variant and complementation group C. The subject's parents were given instructions on protecting him from light and prescribed drugs which will aggravate the DNA repair synthesis deficiency as a result of the G6PD deficiency. XDP is reviewed briefly. (5 Refs)

5. DIFFERENTIAL REACTIVATION OF ZINC-MEDIATED METALLOTHIONEIN INDUCTION IN ULTRAVIOLET-IRRADIATED NORMAL AND REPAIR-DEFICIENT HUMAN CELLS.

Hildebrand CE, Strniste GF

Genetics Group, Los Alamos Natl. Lab., Los Alamos, NM, 87545

J Cell Biochem; 18(1):121-133 1982

Cultured normal human fibroblasts (NF: cell line CRL 1295) and xeroderma pigmentosum (XP) cells (CRL 1223 and XP12BE) were equally sensitive to the cytotoxic effects of zinc chloride ($ZnCl_2$: 5-1,000 uM). Both NF and XP cells tolerated up to 200 uM $ZnCl_2$. In monolayer cultures of either NF or XP cells, the addition of $ZnCl_2$ (200 uM) led to the synthesis of metallothionein (MT). In both cell types, MT synthesis increased from a marginally detectable rate to a max rate (at least 50x the basal rate) within 7 hr. In both cell types, actino-

mycin D (5 ug/ml) inhibited the induction of MT synthesis. In both cell types, exposure to far-UV light before induction with ZnCl2 led to a UV dose-dependent decrease in the max rate of MT synthesis. The XP cells showed a higher UV sensitivity of MT induction than did NF cells. Liquid holding recovery experiments showed that NF cells could reactivate this inducible gene function rapidly, but XP cells were defective in the capacity. If expression of a protein product in a transcriptionally controlled system (MT induction) is used as a direct indicator of damage to the structural gene (transcriptional unit) encoding the protein, the results must be interpreted with caution. Repair processes operating on a time scale comparable to the MT induction process could lead to an underestimation of the size of the UV-sensitive target resulting from reactivation of damaged targets during the induction process. The findings suggest that the transcription unit for thionein induction is a large UV-sensitive target (perhaps greater than 20 kilobases), although the messenger RNA of thionein is much smaller (about 400-500 bases). (33 Refs)

BIOLOGICAL ASPECTS OF DNA ALTERATION AND REPAIR IN RELATION TO MUTAGENICITY

6. SCINTILLOMETRIC DETERMINATION OF DNA REPAIR IN HUMAN CELL LINES: A CRITICAL APPRAISAL.

Bianchi V, Nuzzo F, Abbondandolo A, Bonatti S, Capelli E, Giorio R, Giulotto E, Mazzaccaro A, Stefanini M, Zaccaro L, Zantedeschi A, Levis AG

Istituto di Biologia Animale, Universita di Padova, Via Loredan 10, 35100 Padova, Italy

Mutat Res; 93(2):447-463 1982

The ability of a UV- and x-irradiation and a variety of chemical agents to stimulate DNA repair synthesis in human heteroploid EUE cell cultures was tested by a simplified (3H)thymidine-incorporation scintillometric procedure, with the use of hydroxyurea (HU) to suppress DNA replicative synthesis. The percentage residual DNA synthesis, the absolute increase in DNA radioactivity, as the ratio treated/control, the relative increase in DNA radioactivity, which is an index of DNA repair stimulation, and unscheduled DNA synthesis as measured by autoradiography were determined. The agents used fell into four groups: inhibitors of DNA replication, with evident absolute and relative increases in radioactivity, inhibitors of replication with relative but not absolute increases in radioactivity, compounds not altering any observed parameter, and inhibitors of replication giving negative absolute and relative increases in DNA radioactivity. The procedure described is an improved approach to screening chemicals able to induce DNA repair in mammalian cell cultures, which avoids time-consuming autoradiographic analysis when the scintillometric parameters are definitely positive or negative. (45 Refs)

7. ENHANCED SENSITIVITY TO THE LETHAL AND MUTAGENIC EFFECTS OF PHOTOSENSITIZING ACTION OF CHLORPROMAZINE IN ETHYLENEDIAMINETETRAACETATE-TREATED ESCHERICHIA COLI.

Yonei S, Todo T

Dept. Zoology, Faculty Science, Kyoto Univ., Sakyo-ku, Kyoto 606, Japan

Photochem Photobiol; 35(4):591-592 1982

Ethylenediaminetetraacetate (EDTA) treatment of Escherichia coli H/r30 (Arg-) enhanced cell sensitivity to the lethal and mutagenic effects of the photosensitizing action of chlorpromazine (CPZ). The most obvious effect of EDTA on the fluence-survival curve was an elimination of the shoulder. In the absence of EDTA, CPZ plus near-UV radiation did not induce the reversion from arginine-auxotroph to autotroph of E coli H/r30. However, when EDTA (5 mM)-treated cells were subjected to CPZ plus near-UV radiation, the induced reversion frequency increased with time of irradiation. It is concluded that the enhanced penetration of CPZ into E coli cells by EDTA facilitates the drug binding to DNA within the cells upon near-UV irradiation and that this is the cause for the enhanced photosensitized lethal and mutagenic effects of CPZ. (Author abstract) (9 Refs)

8. THE HELA DNA-SYNTHESIS INHIBITION TEST AS A RAPID SCREEN FOR MUTAGENIC CARCINOGENS.

Painter RB, Howard R

Lab. Radiobiology, Univ. California, San Francisco, CA, 94143

Mutat Res; 92(1/2):427-437 1982

DNA synthesis inhibition (DSI) in HeLa and other mammalian cells was used for rapid detection of relatively strong mutagenic carcinogens. Of 90 agents tested for DSI in HeLa cells, the weaker DNA-damaging agents generally gave positive results only at high doses (1 milliM or greater) and very weak agents (eg, saccharin) gave negative results. One false positive result (cytochalasin B) was observed, with an atypical dose-response curve. The DSI test seems unsuitable for complex mixtures, probably because the DSI activity of a DNA-damaging agent may be masked by the actions of agents without DNA-damaging activity but which inhibit DNA synthesis by other means. (27 Refs)

9. INFLUENCE OF EXPERIMENTAL CONDITIONS AND DNA REPAIR ABILITY ON EMS-INDUCED MUTAGENESIS AND DNA BINDING IN ESCHERICHIA COLI K12: COMPARISON WITH MAMMALIAN CELL MUTAGENESIS.

Mohn GR, Van Zeeland AA, Glickman BW

Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Leiden, The Netherlands

Mutat Res; 92(1/2):15-27 1982

The magnitude of ethyl methanesulfonate (EMS)-induced DNA binding and mutagenesis under different conditions was studied in Escherichia coli K12/343/113, several mutant sublines of this strain, and mammalian cell lines V79 and L5178Y. Under the same exposure conditions (120 min at 37 C, pH 7.2) and at different EMS concentrations (2.5-50 mM), the bacteria and mammalian cells showed similar levels of DNA alkylation (1.7 x 10(-4) -1.5 x 10(-3) ethylations/nucleotide). In stationary E coli cultures, the presence of L-arginine, D-glucose, and fetal calf serum during EMS exposure markedly enhanced the yields of EMS-induced mutations but did not affect the level of

DNA alkylation. Nutrient accumulation by the cells may have enhanced their capacities for genetic fixation and/or phenotypic expression of premutational DNA changes. Because the mammalian cells were significantly more sensitive than repair-proficient E coli to the lethality of a given EMS concentration, the mammalian cells may have a larger genetic and/or physiologic target for cytotoxicity or a lesser ability to repair EMS-induced DNA damage. In bacterial mutants NALr and VALr, and in thioguanine-resistant (hypoxanthine-guanine phosphoribosyltransferase-deficient) and 5-bromo-2'-deoxyuridine-resistant (thymidine kinase-deficient) mammalian cells, low EMS concentrations (up to 7 mM) led to a linear dose-effect (mutation frequency) relationship with no evidence of a threshold. These experiments did not determine whether the very similar dose-effect relationships in E coli and the mammalian cells indicated that the same EMS-induced DNA adducts were responsible for the observed genetic effects. (20 Refs)

10. EVALUATION OF THE CARCINOGENIC POTENTIAL OF 2,4-DINITROFLUOROBENZENE AND ITS IMPLICATIONS REGARDING MUTAGENICITY TESTING.

Warren ST, Dolittle DJ, Chang CC, Goodman JI, Trosko JE
Center for Genetics, Univ. Illinois at the Medical Center, Sch. Basic Medical Sciences, 808 S. Wood St., Chicago, IL, 60612
Carcinogenesis; 3(2):139-145 1982

Tumor promoters are compounds which dramatically enhance the appearance of tumors when chronically applied after an initiating dose of a carcinogen. Initiators are generally considered mutagens while promoters have previously been shown not to induce either DNA damage or mutations. 2,4-Dinitrofluorobenzene (2,4-DNFB), a compound used in the identification of N-terminal amino acids of polypeptides, has been previously reported to be a tumor promoter in mouse skin, while other investigators have found it to be a mutagen in bacteria and yeast. To investigate this apparent discrepancy, we chose to study the carcinogenic potential of 2,4-DNFB utilizing various methods available in V79 Chinese hamster cells. 2,4-DNFB exposure did not result in any unscheduled DNA synthesis, a measure of DNA excision repair, nor did it increase the frequency of sister chromatid exchanges in V79 cells either in the presence or absence of rat liver postmitochondrial supernatant (S-15). Forward mutations in V79 cells, either to ouabain or 6-thioguanine resistance, were not induced by 2,4-DNFB, in the presence or absence of S-15, 2,4-DNFB was, however, able to induce reversions in methionine-requiring E coli auxotrophs in a dose-dependent fashion. Phylogenetic differences between lower organisms and mammals may account for this discordance. 2,4-DNFB was found to inhibit metabolic cooperation, in a dose dependent manner, in V79 cells. This property has previously been shown to be correlated with tumor promoting ability in mouse skin. Therefore, we conclude that the carcinogenic potential of 2,4-DNFB might reside in its ability as a tumor promoter and not as a carcinogenic initiator. Furthermore, these studies serve to illustrate the need for caution when extrapolating bacterial data for risk assessment in humans. (Author abstract) (42 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN VERTEBRATES

11. HEAT MUTAGENESIS OF BACTERIOPHAGE PHIX174 IN SOS-INDUCED BACTERIA.

Schaaper RM, Loeb LA
(c/o Loeb) Dept. Pathology SM-30, Univ. Washington, Joseph Gottstein Memorial Cancer Res. Lab., Seattle, WA, 98195
Mutat Res; 104(1-3):75-78 1982

The effect of heat on intact wild type phiX174 and am3 phage was analyzed. Genetic damage was assumed to include depurination. Am3 was plated on HF4714 (sul+) and wild type was plated on HF4714 (sul+), and Escherichia coli C SOS- and SOS+. Heat treatment of the phage was only weakly mutagenic in normal hosts. In bacteria preirradiated with UV, the reversion frequency increased nearly 100-fold. The rate of inactivation could be closely predicted on the basis of known and extrapolated rates of depurination. (10 Refs)

12. MODULATION OF SURVIVAL AND TRANSFORMATION DURING PLATEAU-PHASE HOLDING OF UV-IRRADIATED MOUSE CELLS.

Chan GL, Little JB
Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
Mutat Res; 104(1-3):183-186 1982

C3H 10T1/2 mouse fibroblasts were cultured for various time periods in the quiescent phase of growth following UV irradiation, to allow DNA repair to occur prior to the initiation of DNA replication. Biological effects of the repair processes were measured with respect to end points of clonogenic survival and malignant transformation. In the first hr of plateau-phase holding after 10 Joules/square meter of UV light, a 1.7-fold survival enhancement was observed, with most of the recovery occurring within the first 6 hr of holding. In experiments where fresh medium was given to 10T1/2 cells during the holding period, the survival enhancement was slightly more than two-fold. In the initial 6 hr of holding, an enhancement in the transformation frequency was observed. In the initial holding period, an error-prone mode of pyrimidine-dimer repair may give rise to both enhanced survival and transformation. The role of pyrimidine dimers in lethality and transformation in 10T1/2 cells is discussed. (17 Refs)

13. IN VIVO AND IN VITRO EFFECTS OF CIGARETTE SMOKE ON CHROMOSOMAL DAMAGE AND SISTER-CHROMATID EXCHANGE IN HUMAN PERIPHERAL BLOOD LYMPHOCYTES.

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Mutat Res; 92(1/2):321-332 1982

The frequencies of chromosomal aberrations in phytohemagglutinin-stimulated peripheral blood lymphocytes (PBL) were studied in 49 women and 47 men (20-75 yr old); 55 were smokers (mostly in the light-to-moderate range, 1-10 cigarettes/day) and 41 were nonsmokers. The mean frequencies of all chromosomal aberrations combined were significantly higher in the smokers than in the nonsmokers (3.20 vs 2.22%). These differences were greatest for the frequencies of interchanges (0.22 vs 0.02%), gaps (0.56% vs 0.24%), fragments (0.67 vs 0.34%), dicentrics (0.42 vs 0.14%), and unambiguous

exchange-type aberrations (0.64 vs 0.17%). A comparison of PBL cultures from a small group of subjects (3 nonsmokers, 3 heavy smokers) showed a 50% higher baseline frequency of sister chromatid exchanges (SCEs) in the smokers (means, 11.6 vs 7.6 SCEs/cell). Exposure to cigarette smoke condensate (CSC: 0.1-1.5 mg/10 ml) caused dose-dependent increases in SCE frequencies in the PBL of both smokers and nonsmokers. The dose-response curves were parallel, suggesting that the apparently greater effects of CSC in causing SCEs in the PBL of smokers simply reflected the higher basal SCE frequencies in this group, although the smokers' PBL showed somewhat more unscheduled DNA synthesis in response to CSC than the nonsmokers' PBL. Mitomycin C (10(-8)-10(-7) M) and ethyl methanesulfonate (10(-4)-10(-3) M) caused dose-dependent increases in the SCE frequencies in PBL from both smokers and nonsmokers. The parallel dose-response curves noted with both agents in both types of PBL suggested that the results reflected the basal differences in SCE frequencies between the groups, as opposed to a greater intrinsic sensitivity to mutagens in the PBL of smokers. (19 Refs)

14. DNA REPAIR AND REPLICATION IN RADIATION-SENSITIVE AND -RESISTANT MOUSE LYMPHOMA CELLS GAMMA-IRRADIATED UNDER AEROBIC AND HYPOXIC CONDITIONS.

Johanson KJ, Wlodek D, Szumiel I
Natl. Defence Res. Inst., S-901 82 Umea, Sweden
Int J Radiat Biol; 41(3):261-270 1982

Repair of DNA damage induced by gamma-rays was studied by the DNA unwinding technique in two strains of murine L5178Y lymphoma cells. These strains differ in sensitivity to low LET radiation by a factor of 1.4. No difference was found in the rate of DNA strand break rejoining during the first 3 hr after irradiation with 2 or 10 Gy of gamma-rays under aerobic conditions either at 0 C or at room temperature. Also, the lesions inflicted by irradiation with 5 Gy of gamma-rays under hypoxia at room temperature were repaired by both strains at the same rate. The final level of unrejoined DNA strand break was the same in both strains, under all conditions examined, within the limits of resolution of the DNA unwinding technique. The rates of DNA chain elongation were also similar in both strains after irradiation under hypoxic or aerobic conditions. (Author abstract) (33 Refs)

15. CELL INJURY AND DNA REPAIR IN X- AND NEUTRON-IRRADIATED CHINESE HAMSTER CELLS.

Korner IJ, Tolkendorf E, Handschack W, Malz W
Central Inst. Molecular Biology, Acad. Sciences GDR, Lindenberger Weg 70, DDR-1115 Berlin, E. Germany
Stud Biophys; 86(1):81-82 1981

Survival rates and chromosome aberrations under oxic and hypoxic conditions and DNA single- and double-strand break rejoining in x- and neutron-irradiated Chinese hamster cells under oxic conditions were investigated. Relative biological effectiveness (RBE) decreased with increasing neutron dose. Survival curves provided an oxygen enhancement ratio of approx 3.0 after x- and 1.9 after neutron-irradiation. The results of chromosome aberrations induction provided the highest RBE for asymmetrical chromosomal exchanges dependent on neutron dose. The higher RBE of the fast neutrons concerning the survival correlated with the rate of chromosome breaks and DNA double-strand breaks and also with a decreased rejoining of single- and double-strand breaks. (5 Refs)

16. PURINE NUCLEOSIDE ANALOGUES INHIBIT THE REPAIR OF RADIATION-INDUCED POTENTIALLY LETHAL DAMAGE IN MAMMALIAN CELLS IN CULTURE.

Nakatsugawa S, Sugahara T, Kumar A
Dept. Experimental Radiology, Faculty Medicine, Kyoto Univ., Kyoto 606, Japan
Int J Radiat Biol; 41(3):343-346 1982

Effects of nucleoside analogs, including 3'-deoxyguanosine, 3'-deoxycytidine, 3'-deoxyuridine, 2',3'-dideoxythymidine, and beta-D-arabinofuranosyladenine, on repair of potentially lethal damage (PLD) in irradiated cells were studied in hamster HA-1 cells in the stationary phase. Of the nucleosides tested, only purine analogs inhibited the repair of PLD significantly at relatively low doses. (10 Refs)

17. RESISTANCE OF 3T3 MOUSE CELLS TO UV LIGHT IN RELATION TO EXCISION AND TRANSFER OF DIMERS TO DAUGHTER STRANDS.

Meneck CF, Meneghini R
Dept. Biochemistry, Inst. Chemistry, Univ. Sao Paulo, Sao Paulo, CP 20780, Brazil
Photochem Photobiol; 35(4):507-513 1982

Mouse cells (3T3 line) and human fibroblasts are equally sensitive to UV light. At fluences of 2.0-2.5 J/m2 mouse cells excise only 20% of the pyrimidine dimers as compared to 80% excised by human fibroblasts. This fluence allows 37% survival in both cases. Hence, mouse cells are more resistant to the same burden of unexcised dimers. The reason for this increased tolerance to dimers does not seem to be due to a recombinational mechanism, as judged by the fact that only ca 5% of the dimers are transferred from parental to daughter strands. The transfer of dimers was measured by the Micrococcus luteus UV endonuclease assay, irradiating cells at G1 to avoid artifacts arising from introduction of dimers in nascent strands. The possibility of other mechanisms being involved in the process of tolerance to DNA lesions is discussed. (Author abstract) (26 Refs)

18. 12-O-TETRADECANOYLPHORBOL-13-ACETATE (TPA) INDUCES SISTER-CHROMATID EXCHANGES AND DELAYS IN CELL PROGRESSION IN CHINESE HAMSTER OVARY AND HUMAN CELL LINES.

Schwartz JL, Banda MJ, Wolff S
Lab. Radiobiology, Univ. California, San Francisco, CA, 94143
Mutat Res; 92(1/2):393-409 1982

In Chinese hamster ovary (CHO) cells and SV40-transformed human fibroblast cell lines (GM637 and XP12RO), 12-O-tetradecanoylphorbol-13-acetate (TPA: 1.0 nanog-1.0 ug/ml) caused a 20-45% increase in the frequency of sister chromatid exchanges (SCEs). This increase in SCEs was not caused by an impurity in the TPA preparation, or increased 5-bromo-2'-deoxyuridine uptake into DNA; it was independent of the incubation time between TPA exposure and fixation of the cells. Simultaneous exposure to TPA (1.0 ug/ml) and benzo(a)pyrene (BP: 1.7 x 10(-5)-3.3 x 10(-6) M) led to a synergistic SCE induction in CHO cells. No synergism was observed after simultaneous exposure to TPA (1 ug/ml) and mitomycin C (0.03 ug/ml) or UV light. In addition to its weak SCE-inducing effects in CHO cells, TPA alone caused a slight delay in cell cycle progression and markedly enhanced the cell cycle delay induced by BP. The SCE-inducing capacity of TPA in these cells was unrelated to its toxicity, because TPA was not toxic

at the doses used. It also seemed to be unrelated to excision repair capacity, because TPA caused similar increases in SCE frequency in cells which were proficient (GM637), mildly deficient (CHO), and severely deficient (XP12RO) in excision repair. The significance of SCE induction and its relationship to other biologic effects of TPA remain unknown. (40 Refs)

19. ARREST OF CHAIN GROWTH OF REPLICON-SIZED INTERMEDIATES BY APHIDICOLIN DURING RAT FIBROBLAST CELL CHROMOSOME REPLICATION.

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Eur J Biochem; 123(1):15-21 1982

The effect of aphidicolin, a specific inhibitor of DNA polymerase alpha, on size maturation of nascent DNA intermediates was studied in cultured rat fibroblast cells. Results provided the first evidence of DNA synthesis associated with merging of intermediates of larger than replicon size. Aphidicolin at a concentration (1.4 ug/ml) causing 90-95% inhibition of [3H]thymidine incorporation, resulted in accumulation of intermediates of nearly the same size as the replicon (2-5 x 10(7) Da); although the synthesis of short nascent fragments (referred to as Okazaki fragments) continued in the presence of aphidicolin, the rate of their elongation to the replicon size was greatly decreased. On removal of aphidicolin, these accumulated intermediates merged into high-mol wt DNA. This merging of the intermediates was associated with DNA synthesis in gaps between adjacent intermediates, as revealed by photolysis of bromodeoxyuridine-DNA leader with long-wave ultraviolet light; when the cells had been pulse-labeled for 5 min with bromodeoxyuridine immediately after removal of the drug, the large DNA arising from aphidicolin-arrested intermediates was cut into fragments of the original size by long-wave ultraviolet light irradiation. The arrest of chain elongation at the replicon-size by aphidicolin might be due to inhibition of this DNA synthesis in gaps, because aphidicolin did not cause degradation of nascent DNAs. (Author abstract) (37 Refs)

20. EFFECTS OF AMPHIDICOLIN ON REPAIR REPLICATION AND INDUCED CHROMOSOMAL ABERRATIONS IN MAMMALIAN CELLS.

van Zeeland AA, Bussmann CJ, Degrassi F, Filon AR, Van Kesteren-van Leeuwen AC, Palitti F, Natarajan AT
Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Wassenaarseweg 72, 2333 AL Leiden, The Netherlands
Mutat Res; 92(1/2):379-392 1982

In growing cultures of normal human skin fibroblasts (HF) and HeLa cells, aphidicolin (APH: 5 ug/ml) enhanced DNA repair replication after UV exposure. In confluent HF cultures, APH inhibited UV-induced repair replication. This inhibitory effect was enhanced in the presence of hydroxyurea (HU: 10 milliM). In confluent HeLa cell cultures, APH inhibited UV-induced repair replication in the presence of HU but enhanced it in the absence of HU. In x-irradiated human peripheral blood lymphocytes (PBL), APH exposure during the G0 or G1 phase increased the occurrence of chromosome breaks and exchanges. The effects of APH on the induction of chromosomal damage in Chinese hamster ovary (CHO) cells depended on the cell cycle stage. In synchronized CHO cells, APH did not significantly affect the frequencies of chromosomal aberrations induced by exposure to x-rays during G2. In G2 cells, APH enhanced the frequencies of x-ray-induced chromatid breaks. In CHO cells exposed to UV, mitomycin C, monofunctional mitomycin C, or 4-nitroquinoline 1-oxide during G1 and exposed to APH in G2 (just before fixation), the frequencies of chromosomal aberrations were higher than in cells exposed only to UV or the alkylating agents. Despite the difficulty of making direct comparisons between the effects of APH on DNA-repair replication and the frequencies of induced chromosomal aberrations, these results indicate that cell type and cell cycle stage influence the biologic responses to APH. (18 Refs)

21. POLY(ADP-RIBOSYLATION) IN N,N-DIETHYLNITROSAMINE-TREATED MICE.

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Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Int J Biochem; 14(3):231-233 1982

C3H mice were treated with single injections of N,N-diethylnitrosamine (DEN: 35-100 mg/kg body wt, ip). Liver nuclei of the treated animals were examined for poly(ADP-ribose) and the conjugate enzyme poly(ADP-ribose) polymerase. The poly(ADP-ribose) content increased with time, showing a peak at about 4 hr post-injection and subsequently falling to pre-injection levels. This effect was dose dependent and was not observed in a control experiment which examined the nuclei of the kidney, a non-target tissue of DEN. The level of poly(ADP-ribose) polymerase also exhibited a transitory increase which was dose dependent. The return of poly(ADP-ribose) levels to the pre-injection level is probably not due to the accompanying loss of polymerase activity but instead to the transient induction of poly(ADP-ribose) glycohydrolase. DEN and other N-nitroso compounds are thought to exert their carcinogenicity via alkylation of DNA. Thus, the measurement of poly(ADP-ribose) and/or its polymerase may provide a basis for measuring DNA damage resulting from carcinogen exposure. (28 Refs)

22. DEFICIENT REPAIR OF CHEMICAL ADDUCTS IN ALPHA DNA OF MONKEY CELLS.

Zolan ME, Cortopassi GA, Smith CA, Hanawalt PC
Dept. Biological Sciences, Stanford Univ., Stanford, CA, 94305-2493
Cell; 28(3):613-619 1982

We have examined excision repair of DNA damage in the highly repeated alpha DNA sequence of cultured African green monkey cells. Irradiation of cells with 254 nm ultraviolet light resulted in the same frequency of pyrimidine dimers in alpha DNA and the bulk of the DNA. The rate and extent of pyrimidine dimer removal, as judged by measurement of repair synthesis, was also similar for alpha DNA and bulk DNA. In cells treated with furocoumarins and long-wave-length ultraviolet light, however, repair synthesis in alpha DNA was only 30% of that in bulk DNa, although it followed the same time course. We found that this reduced repair was not caused by different initial amounts of furocoumarin damage or by different sizes of repair patches, as we found these to be similar in the two DNA species. Direct quantification demonstrated that fewer furocoumarin adducts were removed from alpha DNA than from bulk DNA. In cells treated with another chemical DNA-damaging agent, N-acetoxy-2-acetylaminofluorene, repair synthesis in alpha DNA was 60% of that in bulk DNA. These results show that the repair of different kinds of DNA damage can be affected to different extents by some property of this tandemly repeated heterochromatic DNA. To our knowledge, this is the first demonstration in primate cells of differential repair of cellular DNA sequences. (Author abstract) (33 Refs)

23. DNA REPAIR AND RADIOSENSITIVITY OF CELLS.

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Inst. Medical Radiology, Acad. Medical Sciences USSR, USSR-249 020 Obninsk, USSR
Stud Biophys; 86(1):73-74 1981

DNA damage and the type of DNA lesion leading to cell death were studied. Mouse lymphosarcoma cell line LL was logarithmically cultured after irradiation with 60Co gamma-rays. The cells had the ability to eliminate sublethal and potentially lethal damage and to repair the single- and double-strand DNA breaks and lesions of DNA-membrane complexes, and had the capacity to initiate DNA replication at new replicons. The repair kinetics of cell injuries and DNA repair were near exponential. The process of the single-strand break repair had two components, slow and fast. Results indicated that sublethal injuries may be in the regions of the relaxation of supercoiled DNA. (1 Ref)

24. VALIDATION OF A DNA-REPAIR SYNTHESIS ASSAY ON POOLS OF FRESH AND FROZEN-THAWED LYMPHOCYTES.

Capelli E, Stefanini M, Giulotto E, Nuzzo F
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Mutat Res; 104(1-3):187-191 1982

The possibility of measuring [3H]thymidine incorporation (HTI) stimulated by various treatments was studied in human lymphocyte pools, both fresh and thawed, after storage in liquid nitrogen. For each experiment cells obtained from 4-6 blood samples were mixed in equal proportions prior to exposure. Reagent grade purity chemicals and ranges tested were ethyl methanesulfonate (EMS) 5-20 milliM (mM), methyl methanesulfonate (MMS) 0.5-4 mM, epichlorhydrin (ECCH) 10(-4)-10(2) mM, mitomycin C (MC) 10(-6)-10(2) mM, hycanthone (HY) 10(-2)-2 mM, and cycloheximide (CHX) 3.5 x 10(-3)-3.5 x 10(-2) mM. Repair synthesis was expressed as the difference between HTI values in the presence of hydroxyurea (HU) in treated and untreated cells. CHX reduced HTI without any stimulation of repair. MMS, EMS, and ECCH induced repair synthesis at various concentrations, irrespective of the degree of inhibition of duplicative synthesis. HY inhibited DNA synthesis and induced a slight HTI increase only at 0.1 mM. MC reduced DNA synthesis at the highest concentration assayed and did not significantly increase the HTI rate in the presence of HU. Mean values of repair synthesis obtained with agents in different experiments are presented. The mean cell viability after thawing was 97.2% and decreased with incubation time (84.4% after 24 hr at 37 C). Repair synthesis activity was always present. HTI values in irradiated cells, both in the presence and absence of HU were always higher than in control cells. Results indicate that pools human lymphocytes can be used as an alternative to heteroploid cell lines and diploid fibroblasts in DNA-repair assays. (13 Refs)

25. INHIBITORS OF REPAIR DNA SYNTHESIS.

Collins AR, Squires S, Johnson RT
Cancer Res. Campaign Mammalian Cell DNA Repair Group, Dept. Zoology, Univ. Cambridge, Downing St., Cambridge, CB2 3EJ, England
Nucleic Acids Res; 10(4):1203-1213 1982

We have measured repair DNA synthesis in UV-irradiated normal human fibroblasts, grown to a defined state of quiescence in order to avoid the problem of discriminating repair from replication DNA synthesis. We have assessed the effects of various DNA synthesis inhibitors on repair. Inhibition of repair synthesis by hydroxyurea, 1-beta-D-arabinofuranosylcytosine and aphidicolin is associated with the ability to accumulate DNA breaks due to enzymic incision at DNA damage sites; the inhibition by novobiocin is in accord with its known ability to block incision. (Author abstract) (28 Refs)

26. AN ALKALINE SEPARATION METHOD FOR DETECTION OF SMALL AMOUNT OF DNA DAMAGE.

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Dept. Radiation Biophysics, Faculty Medicine, Univ. Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan
J Radiat Res (Tokyo); 22(4):415-424 1981

The alkaline separation method for detection of DNA damage was made quantitative by calibration with an alkaline sucrose gradient centrifugation, and applied to analysis of DNA damage in cultured mouse leukemic L5178Y cells after x-irradiation. The new method can detect DNA damage, probably scissions and alkali-labile sites, but not sinlge- and double-strand breaks. The method can also detect DNA damage due to ethyl methanesulfonate or 4-nitroquinoline 1-oxide. (14 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN INVERTEBRATES AND LOWER EUKARYOTES

27. PLATE ASSAY FOR CHEMICAL- AND RADIATION-INDUCED MUTAGENESIS OF CAN1 IN YEAST AS A FUNCTION OF POST-TREATMENT DNA REPLICATION: THE EFFECT OF RAD6-1.

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Biology Div., Oak Ridge Natl. Labs., Oak Ridge, TN, 37830
Mutat Res; 93(2):339-352 1982

In order to monitor the yield of induced can1 mutants of Saccharomyces cerevisiae before, during, and after the first round of post-treatment DNA replication, a method was developed. Mutagen-treated stationary-phase cells were permitted to divide on synthetic agar growth medium for varying time periods before mutant selection with top agar medium containing L-canavanine (CAN). With the CAN overlay method the initial number of viable cells plated remains constant so that an increased mutant yield with time should reflect a component of mutagenic potential requiring DNA replication. The predominant component of UV- and hydrazine (HZ)-induced CAN1 mutagenesis appears pre-replicative and replicative (or post-replicative), respectively. The advantage of the overlay method is that it permits observation of the kinetics of induced mutation at CAN1 in relation to post-treatment DNA replication in the absence of exogenous inhibitory substances. The rad6-1 allele significantly reduces frequencies of both UV- and HZ-induced mutagenesis at CAN1; experiments involving both liquid and agar post-treatment showed that the rad6-1 defect in UV mutagenesis cannot be alleviated by allowing DNA replication. (14 Refs)

28. THE USE OF A YEAST STRAIN WITH A TEMPERATURE-SENSITIVE DNA LIGASE TO ESTIMATE DNA REPAIR AFTER EXPOSURE TO MUTAGENS.

Tippins RS, Waters R, Parry JM
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Mutat Res; 104(1-3):79-86 1982

DNA repair in yeast was determined at early times after UV irradiation using the Saccharomyces cerevisiae strain cdc9 that has a temperature-sensitive DNA ligase, by measuring the incidence of single-strand breaks that occur during incomplete repair at the restrictive temperature following UV irradiation. Advantages of the technic are listed. The number of strand breaks induced in cdc9 at 37 C equalled the number of UV-induced pyrimidine dimers at low UV doses. The kinetics of DNA repair following treatment with the chemical mutagen 4-chloromethyl-biphenyl were examined. (10 Refs)

29. CYTOTOXIC AND MUTAGENIC EFFECTS OF NEOCARZINOSTATIN IN WILD-TYPE AND REPAIR-DEFICIENT YEASTS.

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Mutat Res; 104(1-3):87-94 1982

Cytotoxic and mutagenic effects of the antitumor protein antibiotic neocarzinostatin (NCS) were studied in the yeast Saccharomyces cerevisiae. Results of exposure to NCS were compared in wild-type RAD+, rad52 mutants defective in repair of double-strand DNA breaks, rad3 mutants defective in excision repair of UV-induced pyrimidine dimers, and rad3 rad52 double mutants. Holo-NCS was isolated and purified from cultures of Streptomyces carzinostaticus. Holo-NCS was shown to be free of contamination by apo-NCS. Yeast cultures were exposed to NCS in various concentrations for 24 hr. Growth of RAD+ or rad3 cultures was inhibited only slightly at NCS concentrations up to 100 ug/ml. Rad52 cultures and rad3 rad52 were strongly inhibited by concentrations as low as 1 ug/ml. Inhibition showed an apparent saturation effect below 25 ug/ml. Culture doubling time was doubled in rad52 and rad3 rad52 cultures at 5 ug/ml relative to control. NCS produced a cytostatic effect and, at high concentrations, a cytotoxic effect. Studies using 125I-labeled NCS indicated that uptake of NCS was approx equal in RAD+ and rad52 strains, indicating that growth inhibition resulted from repair defects rather than cellular penetration by NCS. Cytotoxicity occurred primarily in dividing cells. Studies using differential minimal media indicated that NCS produced reversions at the his1-7 and lys1-1 loci. Results indicate induction of repairable DNA damage (double-strand breakage) by NCS in eukaryotic cells. Possible carcinogenicity of NCS is suggested. (38 Refs)

30. GENETIC AND BIOCHEMICAL CONSEQUENCES OF THYMIDYLATE STRESS.

Barclay BJ, Kunz BA, Little JG, Haynes RH
Dept. Biological Sciences, Brock Univ., St. Catherines, Ontario L2S 3A1, Canada
Can J Biochem; 60(3):172-194 1982

We have examined the genetic and biochemical consequences of thymidylate stress in haploid and diploid strains of the simple eukaryote Saccharomyces cerevisiae (Bakers' yeast). Previously we reported that inhibition of dTMP biosynthesis causes 'thymineless death' and is highly recombinagenic, but apparently not mutagenic, at the nuclear level; however, it is mutagenic for mitochondria. Concurrent provision of dTMP abolishes these effects. Conversely, excess dTMP is highly mutagenic for nuclear genes. It is likely that DNA strand breaks are responsible for the recombinagenic effects of thymidylate deprivation; such breaks could be produced by reiterative uracil incorporation and excision in DNA repair patches. In our experiments, thymidylate stress was produced both by starving dTMP auxotrophs for the required nucleotide and also by blocking de novo synthesis of thymidylate by various antimetabolites. We found that the antifolate methotrexate is a potent inducer of mitotic recombination (both gene conversion and mitotic crossing-over). This suggests that the gene amplification associated with methotrexate resistance in mammalian cells could arise, in part, by unequal sister-chromatid exchange induced by thymidylate stress. In addition, several sulfa drugs, which impede de novo folate biosynthesis, also have considerable recombinagenic activity. (Author abstract) (138 Refs)

31. POSTREPLICATION REPAIR IN NEUROSPORA CRASSA.

Calza RE, Schroeder AL
Program in Genetics and Cell Biology, Washington State Univ., Pullman, WA, 99164
MGG; 185(1):111-119 1982

Changes in the mol wt of nascent DNA made after ultraviolet (UV) irradiation have been studied in the excision-defective Neurospora mutant uvs-2 using isotopic pulse labeling, alkaline gradient centrifugation and alkaline filter elution. Both the size of nascent DNA and the rate of incorporation of label into DNA was reduced by UV light in a dose dependent manner. However, this DNA repair mutant did recover the ability to synthesize control-like high mol wt DNA 3 hr after UV treatment, although the rate of DNA synthesis remained depressed after the temporary block to elongation (or ligation) had been overcome. Photoreactivation partially eliminated the depression of DNA synthesis rate and UV light killing of cells, providing strong evidence that the effects on DNA synthesis and killing were caused by pyrimidine cyclobutane dimers. The caffeine inhibition repair studies performed were difficult to quantitate but did suggest either partial inhibition of a single repair pathway or alternate postreplication DNA repair pathways in Neurospora. No enhancement in killing was detected after UV irradiation when cells were grown on caffeine containing plates. (Author abstract) (57 Refs)

32. ENHANCEMENT OF ULTRAVIOLET OR N-METHYL-N'-NITRO-N-NITROSOGUANIDINE SENSITIVITY OF DICTYOSTELIUM DISCOIDEUM BY 3-AMINOBENZAMIDE.

Ohnishi T, Eimoto H, Okaichi K
Molecular and Cell Biology Program, 201 Althous Lab., Pennsylvania State Univ., University Park, PA, 16802
Photochem Photobiol; 35(4):515-519 1982

The amoeboid cells of Dictyostelium discoideum NC-4 possess a 3-aminobenzamide(3-ABA)-sensitive repair mechanism for DNA damages induced by UV-irradiation or N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)-treatment. We have studied the effect of 3-ABA on each step of excision repair in the UV-irradiated cells. Although the nicking of DNA-strand and the excision of pyrimidine dimers are insensitive to 3-ABA, the rejoining of DNA strand-breaks is sensitive. The frequency of mutation induced by UV-irradiation or MNNG-treatment is depressed by 3-ABA. The mechanisms of repair inhibition by 3-ABA are discussed. (Author abstract) (24 Refs)

33. EFFECT OF HEAT SHOCK ON POLY(ADP-RIBOSE) SYNTHETASE AND DNA REPAIR IN DROSOPHILA CELLS.

Nolan NL, Kidwell WR
Lab. Pathophysiology, NCI, NIH, Bethesda, MD, 20205
Radiat Res; 90(1):187-203 1982

The capacity of Drosophila cells to repair gamma-ray induced DNA lesions using the quantity of poly(ADP-ribose) synthetase (PARS) left after heat shock (37 C) was investigated. PARS was not necessary for rejoining gamma-ray induced DNA strand breaks. Inhibitors of PARS, 3-aminobenzamide and 5-methyl nicotinamide, lowered the PARS level in whole cells and prevented an increase in polymer levels following irradiation, without blocking the rejoining of gamma-ray-induced DNA strand breaks. (58 Refs)

34. A SEARCH FOR SOME COMMON CHARACTERISTICS OF THE EFFECTS OF CHEMICAL MUTAGENS IN DROSOPHILA.

Vogel EW, Blijleven WG, Kortselius MJ, Zijlstra JA
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Mutat Res; 92(1/2):69-87 1982

An analysis of shared general features was used to compare the actions of mutagens in Drosophila. Germ cell metabolism is the most significant factor determining the effects of promutagens in various cell stages. Only autosomal recessive lethal mutations can be used to compare stages sensitivity to a given mutation. Only a few mutagens have been tested in both sexes of Drosophila, including mitomycin C, bleomycin (BLM), and diethylstilbestrol. Females are much more sensitive than males to the mutagenic action of BLM, which causes recessive lethals and X-chromosomal aneuploidy in oocytes. The mutagenicities of some (not all) alkylating agents can be greatly modified by introducing repair-deficient mutants into the test system, but each new strain must be validated before it is tested with a wide variety of mutagens. The molecular mechanisms of the interactions of some methylating and ethylating agents with DNA are related to their genetic effects in germ cells. The relative proportions of chromosome aberrations to mutations and the ability of an agent to induce delayed mutations can be used to provide more information on the basic mechanisms of chemical mutagenesis. For at least some mutagens, a positive correlation has been discovered between the induction of chromosome aberrations in germ cells and the induction of an increased proportion of mosaic twin spots (relative to mosaic single spots) in somatic tissues. (68 Refs)

35. THE MUTAGENIC EFFECTS OF DIEPOXYBUTANE IN WILD-TYPE AND MUTAGEN-SENSITIVE MUTANTS OF DROSOPHILA MELANOGASTER.

Olsen OA, Green MM
Inst. General Genetics, Univ. Oslo, P.O. Box 1031 Blindern, Oslo 3, Norway
Mutat Res; 92(1/2):107-115 1982

The effects of 1,2,3,4-diepoxybutane (DEB) on two X-chromosome loci (w and y) of Drosophila were studied. At least one-third of the DEB-induced mutations were chromosome deletions. The nature of the DEB-induced complementary mutants was not clear. Some of the mutants were mosaics, expressed somatically but not transmitted in the germ line. Somatic sensitivity to DEB was demonstrated by 9/11 methyl methanesulfonate (MMS)-sensitive mutants. The MMS-sensitive and DEB-insensitive mutants were also somatically insensitive to nitrogen mustard and UV (one was also insensitive to x-rays), suggesting that these mutants (mus103 and mus105) may not be involved in DNA replication or repair. In direct genetic experiments, females homozygous for at least 2/6 and probably 5/6 MMS-sensitive mutants showed an impaired capacity to repair DEB-induced damage in spermatozoa. Females homozygous for MMS-sensitive mutant mus201 showed an unimpaired capacity to repair DEB-induced genetic damage. (15 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN BACTERIA

36. A BACTERIOPHAGE T4 MUTANT DEFECTIVE IN BOTH DNA REPLICATION AND REPLICATION REPAIR.

Cupido M, Schreij-Visser O, Van der Ree P
Dept. Radiation Genetics and Chemical Mutagenesis, Wassenaarseweg 72, Leiden, The Netherlands
Mutat Res; 93(2):285-295 1982

The bacteriophage T4 mutant uvs57 is characterized. The mutation causes arrest of DNA synthesis at 25 and 30 C. Mapping, crossing, multiplication, recombination, UV-sensitivity, fidelity and kinetics of DNA replication, and release of progeny DNA from the host-cell membrane are described. Repair of UV-induced lesions by T4 is discussed. (36 Refs)

37. PRODUCTION OF PLASTIDIAL ANTIBIOTIC-RESISTANT MUTANTS BY ULTRAVIOLET IRRADIATION OF EUGLENA GRACILIS.

Nicolas P, Nigon V
Departement de Biologie generale et appliquee, Universite Claude-Bernard Lyon I, 43, boulevard du 11 novembre 1918, F-69622 Villeurbanne Cedex, France
MGG; 185(1):184-185 1982

Ultraviolet-irradiation of Euglena gracilis drastically increases the proportion of green colonies resistant to chloroplast-inhibiting antibiotics. Some green colonies persist at high UV doses. These results might indicate the occurrence in the chloroplastic DNA of repair processes, of which one could be error-prone. (Author abstract) (17 Refs)

38. CLONED TRUNCATED RECA GENES IN E. COLI. I. EFFECT ON RADIOSENSITIVITY AND RECA+ DEPENDENT PROCESSES.

Sedgwick SG, Yarranton GT
Genetics Div., Natl. Inst. Medical Res., London NW7 1AA, England
MGG; 185(1):93-98 1982

Plasmids pMH1 and pDR1461, possessing the control region and 22% or 73% of the Escherichia coli recA gene, conferred UV sensitivity to wild-type uvrA, and umuC bacteria. Sensitization was less in recA441 (tif-1) mutants and absent in lexA cells. Radiosensitization correlated with inhibition of recombinational repair, even through induced recA protein synthesis and recombination in Hfr matings were normal. Plasmids pMH1 and pDR1461 also prevented induction of some, but not all, SOS functions. Mutagenic reversion to tryptophan prototrophy and induced reactivation of UV-irradiated phage lambda were eliminated, and the efficiency of lambda lysogenic induction reduced. However, naladixic acid induced filamentous growth, mitomycin-C induced uvrA gene expression and

post UV-irradiation DNA degradation control were little changed. Explanations of these effects are discussed which involve the presence of either truncated recA protein or multiple copies of the recA gene control sequence. (Author abstract) (41 Refs)

39. CLONED TRUNCATED RECA GENES IN E. COLI. II. EFFECTS OF TRUNCATED GENE PRODUCTS ON IN VIVO RECA+ PROTEIN ACTIVITY.

Yarranton GT, Sedgwick SG
Genetics Div., Natl. Inst. Medical Res., London NW7 1AA, England
MGG; 185(1):99-104 1982

The ability of plasmids carrying truncated recA genes to sensitize recA+ cells to UV-irradiation was dependent upon the size of the cloned recA gene fragment. Radiosensitization correlated with the inhibition of recombinational repair, and the in vivo reduction of recA protein recombinase activity, as measured by lambdabio11 plating efficiency. W-reactivation was also abolished by the radiosensitizing plasmids, while DNA degradation control, naladixic acid induced filamentation and lambda induction were unaffected. UV-induced mutagenesis in excision proficient Escherichia coli was unaffected, while excision deficient strains were hypermutable. It is suggested that these effects of plasmids bearing 22% or more of the recA gene are the result of the interaction of full-sized and truncated protein subunits to generate multimers unable to catalyze recombination. (Author abstract) (14 Refs)

40. A NEW PATHWAY FOR REPAIR OF CROSS-LINKABLE 8-METHOXYPSORALEN MONO-ADDUCTS IN UVR- STRAINS OF ESCHERICHIA COLI.

Bridges BA, Stannard M
MRC Cell Mutation Unit, Univ. Sussex, Falmer, Brighton, Sussex, BN1 9QG, England
Mutat Res; 92(1/2):9-14 1982

In three Uvr-families of Escherichia coli, a metabolic process was discovered involving certain mono-adducts of 8-methoxypsoralen (8-MOP) in DNA, leading to a loss of their ability to form lethal cross-links after UV exposure, removal of unbound 8-MOP, and another exposure to near UV after a variable recovery period. This process was dependent on the polA+ gene (DNA polymerase), but not on protein synthesis or DNA replication. It seemed to be a repair pathway, independent of uvrAB endonuclease, initiated either by a different endonuclease or an N-glycosylase. This repair process was not affected by a rep gene mutation and thereby differed from the uvrA+-independent cross-link repair pathway, but the results did not exclude the possibility that a common enzyme may be involved. (12 Refs)

41. RESIDENT ENHANCED REPAIR: NOVEL REPAIR PROCESS ACTION ON PLASMID DNA TRANSFORMED INTO ESCHERICHIA COLI K-12.

Strike P, Roberts J
Dept. Genetics, Univ. Liverpool, Liverpool L69 3BX, England
J Bacteriol; 150(1):385-388 1982

The survival of UV-irradiated DNA of plasmid NTP16 was monitored after its transformation into recipient cells containing an essentially homologous undamaged plasmid, pLV9. The presence of pLV9 resulted in a substantial increase in the fraction of damaged NTP16 molecules which survived in the recipient cells. This enhanced survival requires the host uvrA+ and uvrB+ gene products, but not the host recA+ gene product. The requirement for both homologous DNA and the uvrA+ and uvrB+ gene products suggests that a novel repair process may act on plasmid DNA. Possible mechanisms for this process are considered. (Author abstract) (14 Refs)

MACROMOLECULAR BINDING OF CARCINOGENS

42. BENZPYRENE GROUPS BIND PREFERENTIALLY TO THE DNA OF ACTIVE CHROMATIN IN HUMAN LUNG CELLS.

Arrand JE, Murray AM
Dept. Biochemistry, St. Mary's Hosp. Medical Sch., London W2 1PG, England
Nucleic Acids Res; 10(5):1547-1555 1982

The cells of the bronchial epithelium of man are targets for benzo(a)pyrene carcinogenesis. When cultures of these cells, and of non-target fibroblasts, are exposed to [3H]benzo(a)pyrene, we find that the epithelial cells metabolize and bind to DNA far greater amounts of benzpyrene than do fibroblasts. By analysis of nuclei of benzyprene-treated cells for sensitivity to limited digestion with pancreatic DNase I, we have shown that benzpyrene groups bind initially to the DNA of expressed (DNase I sensitive) regions of chromatin in both cell types. Covalent binding of benzpyrene groups to nonexpressed (DNase I resistant) regions follows rapidly in the target epithelial cells. These maintain high levels of carcinogen adducts in their DNA. In fibroblasts, benzyprene group binding to non-expressed DNA occurs more slowly and active removal of adducts from the DNA is evident. (Author abstract) (21 Refs)

43. CARCINOGENIC EPOXIDES OF BENZO[A]PYRENE AND CYCLOPENTA[CD]PYRENE INDUCE BASE SUBSTITUTIONS VIA SPECIFIC TRANSVERSIONS.

Eisenstadt E, Warren AJ, Porter J, Atkins D, Miller JH
Dept. Microbiology, Harvard Sch. Public Health, Boston, MA, 02115
Proc Natl Acad Sci USA; 79(6,part1):1945-1949 1982

We have determined the spectrum of base-pair substitution mutations induced in the lacI gene of uvB- strain of Escherichia coli by two polycyclic aromatic hydrocarbons (+-)7alpha,8beta-dihydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydrobenzo[a]pyrene (BPDE), and 3,4-epoxycyclopenta[cd]pyrene (CPPE). Approximately 10% of all lacI mutations induced by either BPDE or CPPE are nonsense mutations, suggesting that base-pair substitutions are a large fraction of the mutational events induced by these agents in the uvB- bacteria. Both carcinogens specifically induced the G-C to T-A and, to a lesser extent, the A-T to T-A transversions. One possible mechanism for transversion induction at G-C sites by BPDE might involve carcinogen binding to the exocyclic amino group of guanine in the template strand followed by a rotation of the modified base around its glycosylic bond from the anti to the syn conformation. This could allow specific pairing of modified bases with an imino tautomer of adenine. (Author abstract) (26 Refs)

44. ANALYSIS OF N-ACETOXY-N-2-ACETYLAMINOFLUORENE-INDUCED FRAME-SHIFTS IN PBR322.

Yoon K, Shelegedin VN, Kallenbach NR

Center Oral Health Res., Sch. Dental Medicine, Univ. Pennsylvania, Philadelphia, PA, 19104

Mutat Res; 93(2):273-283 1982

A simple system is described which can be used to study directly the sequence change and cellular functions involved in frame-shift mutagenesis by covalently reactive mutagen. Positive and negative alterations in the number of base pairs of tetracycline resistant gene of pBR322, were created by cutting with Sal restriction enzyme followed by either removal with nuclease Sl or extension with reverse transcriptase, and reclosing by a 'blunt-ended' joining reaction catalyzed by T4 DNA ligase. Mutagenesis in vitro by exposure to N-acetoxy-N-2-acetylaminofluorene (AAAF) was used to cause reversion of frame-shifted plasmid molecules. Transformation of AAAF-reacted frame-shift plasmid DNA into Escherichia coli strains AB1157, AB1886, and AB2463 was performed, and a number of revertants (ApRTcR) not represented in unreacted controls were generated. Differential inactivation of the AP gene was observed among the E coli strains. The system used here is suitable for any chemicals that bind covalently to DNA. (25 Refs)

45. HEPATIC MICROSOMAL METABOLISM AND MACROMOLECULAR BINDING OF THE ANTIOXIDANT, N-PHENYL-2-NAPHTHYLAMINE.

Anderson MM, Mitchum RK, Beland FA

(c/o Beland) Natl. Center Toxicological Res., Food and Drug Admin., Jefferson, AR, 72079

Xenobiotica; 12(1):31-43 1982

The hepatic microsomal metabolism of N-phenyl-2-naphthylamine (P2NA), an industrial antioxidant and suspected carcinogen, was studied in seven mammalian species to determine if N-dephenylation, reported to occur in vivo, could be demonstrated in vitro and if macromolecular binding occurs without an obligatory N-dephenylation. The rate of hepatic microsomal metabolism decreased in the order: hamster very much greater than mouse, greater than rat, approx equal to monkey, approx equal to dog, greater than human, approx equal to pig. Metabolism was increased by pretreatment with 3-methylcholanthrene or phenobarbital and decreased by carbon monoxide or 2-[(2,4-dichloro-6-phenyl)phenoxy]-ethylamine, which indicated the involvement of cytochrome P-450 rather than the flavoprotein mixed-function oxidase. All seven species produced two major metabolites identified as 6-hydroxy-P2NA and 4'-hydroxy-P2NA. The carcinogen 2-naphthylamine was not detected in the microsomal incubations. Incubations in the presence of 18O2 indicated that the oxygen incorporated in the products came from molecular oxygen. There was a time-dependent linear increase in covalent binding of P2NA to microsomal protein and the extent of binding approx paralleled the rate of metabolism. Thus, macromolecular binding of this aromatic amine appears to occur without an obligatory N-dephenylation and may be due to the metabolic formation of epoxides. (Author abstract) (31 Refs)

46. THE METABOLISM AND ACTIVATION OF POLYCYCLIC AROMATIC HYDROCARBONS IN EPITHELIAL CELL AGGREGATES AND FIBROBLASTS PREPARED FROM RAT MAMMARY TISSUE.

Cooper CS, Pal K, Hewer A, Grover PL, Sims P

Chester Beatty Res. Inst., Inst. Cancer Res., Royal Cancer Hosp., Fulham Road, London SW3 6JB, England

Carcinogenesis; 3(2):203-210 1982

The metabolism of 7,12-dimethylbenz[a]anthracene (DMBA), benzo[a]pyrene (BP) and benz[a]anthracene (BA) by epithelial cell aggregates and fibroblasts in culture has been investigated using mammary tissue obtained from female Wistar rats. The results show that (a) both types of mammary cells metabolize all three hydrocarbons into ether- and water-soluble derivatives; (b) the patterns of metabolites produced by epithelial cells and fibroblasts are similar but that fibroblasts form more of the water-soluble materials; (c) the major dihydrodiols formed are the 8,9-dihydrodiols of BA and DMBA and the 7,8-and 9,10-dihydrodiols of BP; (d) all three hydrocarbons are metabolized to form products that bind covalently to protein but only the potent carcinogens BP and DMBA are metabolized to form derivatives that react covalently with DNA; and (e) the chromatographic profiles of the hydrocarbon-deoxyribonucleoside adducts formed in epithelial cells treated with either BP or DMBA are similar to those obtained in analogous experiments with fibroblasts. (Author abstract) (50 Refs)

47. SIMILAR LEVEL OF METABOLIC ACTIVATION OF BENZO(A)PYRENE IN PERFUSED RAT LUNG AND LIVER AND PROTECTION OF LUNG BY LIVER IN A COMBINED PERFUSION SYSTEM.

Klaus E, Foth H, Kahl R, Kahl G

(c/o Kahl, G.) Dept. Pharmacology, Univ. Mainz, Obere Zahlbacher Strasse 67, D-6500, Mainz, Germany

Biochem Biophys Res Commun; 105(2):596-602 1982

The binding of benzo(a)pyrene metabolites to DNA, RNA, and protein in perfused rat liver and lung in situ and the influence of the liver on the level of nucleic acid and protein modification by benzo(a)pyrene in the lung were investigated. In the liver of 5,6-benzoflavone pretreated rats, irreversible binding of metabolically activated benzo(a)pyrene to both nucleic acids and protein reaches a peak at 15 min and then declines. In contrast, binding in the lung continuously increases over the 2 hr perfusion period. The extent of binding is of the same order of magnitude in the liver and lung of cytochrome P-448-induced (ie 5,6-benzoflavone-induced) animals. At 15 min, binding to both DNA and RNA in the liver exceeds binding to nucleic acids of the lung by a factor of 3-6; this relations is nearly reversed after 2 hr of perfusion. Protein binding is more pronounced in the lung than in the liver over the entire 2 hr perfusion. The longer persistance of benzo(a)pyrene binding in the lung may contribute to the fact that the lung and not the liver is the target organ of benzo(a)pyrene carcinogenesis. Following the insertion of a liver into the perfusion circuit of the lung, the total irreversible binding of metabolically activated benzo(a)pyrene to DNA, RNA, and protein is reduced, this effect being more pronounced in 5,6-benzoflavone-induced animals. Thus the high detoxication capacity of the liver can protect other organs having lower xenobiotic metabolizing activity against benzo(a)pyrene. (16 Refs)

EFFECT OF CARCINOGENS ON MACROMOLECULAR SYNTHESES

48. STUDIES ON TUMORIGENICITY AND METABOLISM OF ISONIAZID IN MICE AND RATS.

Mate NB, Maru GB, Bhide SV
Carcinogenesis Div., Cancer Res. Inst., Tata Memorial Centre, Bombay 400 012, India
Indian J Exp Biol; 19(11):1037-1039 1981

The carcinogenicity and metabolism of isoniazid (INH) and its effect on nucleic acid and protein biosynthesis were studied in Wistar rats and Swiss mice. Mice received 1.1 mg INH/day and rats 4 mg/day by gavage, or mice and rats received 0.09 mg/kg body wt ip. Rats treated with INH were refractory to the tumorigenic effect of the drug. INH was tumorigenic only in mice, with a 55% incidence of lung tumors. In mice, there was a significant increase in ammonia levels occurred 1 hr after administration and remained high even at 4 hr; no increase in ammonia was noted at any time in rats. The concentration of circulating INH was much higher in mice than in rats at different time points. Levels of acetyl isoniazid were higher in rats than mice, suggesting faster acetylation in rats than mice. In mice, circulating levels of mono and diacetyl hydrazines remained high for longer periods than in rats. INH and hydrazine sulfate inhibited DNA synthesis in lung tissue of mice only, while not affecting DNA biosynthesis in mouse liver and the lung and liver of rats. Acetyl isoniazid had no inhibitory effect on any of the tissues of the rat. Two hr after INH administration, protein biosynthesis was not affected in liver and lung tissues of mice, although 24 hr after administration protein synthesis was inhibited in lung tissue. Rat tissues were not affected with respect to DNA synthesis. (24 Refs)

49. A REDUCED CAPACITY FOR UNSCHEDULED DNA SYNTHESIS IN LYMPHOCYTES FROM INDIVIDUALS EXPOSED TO PROPYLENE OXIDE AND ETHYLENE OXIDE.

Pero RW, Bryngelsson T, Widegren B, Hogstedt B, Welinder H
Wallenberg Lab., Biochemical and Genetic Ecotoxicology, Univ. Lund, Box 7031, S-220 07 Lund 7, Sweden
Mutat Res; 104(1-3):193-200 1982

Inhibition of unscheduled DNA synthesis (UDS) was studied in 23 workers (25-59 yr old, mean age 41 yr) exposed to propylene oxide (PO) as process workers for 1-20 yr (mean 10 yr) and in 5 male workers (25-44 yr old, mean age 32 yr) exposed to ethylene oxide (EO) as sterilizing, packing, or truck-driving personnel for 0.3-5 yr (mean 2.9 yr). Eighteen of 23 PO-exposed workers were smokers. Controls were 12 male workers (21-46 yr old, mean age 30 yr) not exposed occupationally to any mutagenic chemical compound. Five of the controls were smokers. UDS induced by N-acetoxy-2-acetylaminofluorene (NA-AAF) and NA-AAF binding to DNA were the methods used. Use of [3H]NA-AAF enabled the direct assessment of initial NA-AAF damage to DNA, which in turn served as the substrate for induction of UDS, and thereby repair of NA-AAF lesions in the DNA. Lymphocyte samples from both the controls and the PO-exposed workers varied considerably in values for NA-AAF-induced UDS. UDS variation was dependent on the level of NA-AAF bound to DNA after a 30-min incubation of lymphocytes in the presence of 10 uM [3H]NA-AAF. The correlation coefficients between NA-AAF-induced UDS and NA-AAF binding to DNA were highly significant for both the controls and PO-exposed workers. PO-plus EO-exposed workers exhibited significant reductions in NA-AAF-induced UDS when compared to the controls. The level of [3H]NA-AAF covalent binding to DNA was not significantly reduced by PO- and EO-exposure. Results indicate that exposure to relatively low doses of PO and EO can cause individuals to be at increased risk due to a reduced capacity to repair DNA lesions. (12 Refs)

50. POLYSOMAL POLYADENYLATED RNA AND ALBUMIN MESSENGER RNA IN MASTOMYS LIVER AND IN A CHEMICALLY INDUCED HEPATOCELLULAR CARCINOMA.

Krieg L, Krause-Leipholdt D, Wayss K, Volm M
Institut fur Experimentelle Pathologie, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld, D-6900 Heidelberg, W. Germany
Cancer Res; 42(5):1986-1993 1982

A hepatocellular carcinoma line (H78) was established from a primary liver tumor induced in Mastomys natalensis by a single administration of dimethylnitrosamine. Six to 8 mo after transplantation (passages 5 to 7), well-differentiated tumors, still containing glycogen-storing cells, were isolated and used for the preparation of RNA. Polysomal polyadenylated RNAs from Mastomys liver and from the H78 tumor line were then compared by hybridization kinetics. Total kinetic complexities were 6.6 x 10(9) and 6.3 x 10(9) daltons for liver and tumor, respectively. Complexities of the high and middle abundant class were reduced in the hepatoma. Heterologous hybridization reactions revealed that, in terms of RNA mass, all or most of the polysomal polyadenylated RNA present in the liver was also present in the tumor and vice versa. However, shifts in the relative abundance of messenger RNA sequences were detected. In contrast to most other transplanted hepatomas, H78 has approx the same content of albumin messenger RNA on its polysomes as has untreated liver. (Author abstract) (44 Refs)

51. INHIBITION OF MITOCHONDRIAL PROTEIN SYNTHESIS DURING EARLY STAGES OF AFLATOXIN B1-INDUCED HEPATOCARCINOGENESIS.

Bhat NK, Emeh JK, Niranjan BG, Avadhani NG
(c/o Avadhani) Lab. Biochemistry, Dept. Animal Biology, Sch. Veterinary Medicine, Univ. Pennsylvania, Philadelphia, PA, 19104
Cancer Res; 42(5):1876-1880 1982

Experiments were designed to determine the in vivo effects of a single 6-mg/kg dose aflatoxin B1 on rat liver mitochondrial transcription and translation processes. With the use of intact hepatocytes and also a highly active mitoplast system for incorporation, it was observed that both mitochondrial transcription and translation activities are inhibited progressively even after 24 hr of carcinogen administration. Electrophoretic patterns of mitochondrial translation products show some qualitative changes during early periods of carcinogen administration. At later stages (greater than 12 hr), however, there is a general inhibition of many of the products, although by this time there is a qualitative and quantitative recovery in the synthesis of mitochondrial proteins imported from the cytoplasm. These results, along with the data showing considerably high levels of aflatoxin B1 binding to mitochondrial DNA suggest that mitochondrial genetic system is one of the direct targets during experimental carcinogenesis. (Author abstract) (31 Refs)

REVIEWS

52. STUDIES ON THE MECHANISMS INVOLVED IN MULTISTAGE CARCINOGENESIS IN MOUSE SKIN.

Slaga TJ, Fischer SM, Weeks CE, Klein-Szanto AJ, Reiners J
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
J Cell Biochem; 18(1):99-119 1982

Skin tumors can be induced in of mice by repeated applications of a carcinogen (complete carcinogenesis) or one subthreshold dose of a carcinogen followed by repeated applications of a weak or noncarcinogenic tumor promoter (initiation-promotion carcinogenesis). Of several mouse strains studied, Sencar was the most sensitive to both types of carcinogenesis. An important aspect of tumor initiation by polycyclic aromatic hydrocarbons (PAH) is their metabolism to an electrophilic intermediate(s) which interacts covalently with epidermal DNA. Tumor promotion can be divided into at least two stages: the first obtainable by limited treatment with 12-O-tetradecanoylphorbol-13-acetate (TPA) or certain nonpromoters; the second obtainable by repeated applications of mezerein. The dark basal keratinocytes (primitive stem cells) are important in the first stage of promotion. Most of the other cellular and biochemical events associated with promotion are actually associated with the second stage. Some evidence has been found suggesting that strain and/or stock differences in responses to complete and/or multistep carcinogenesis represent differences in responses to complete and/or promotion. Although C57BL/6 mice are relatively resistant to PAH initiation and phorbol ester promotion, they are fairly sensitive to complete carcinogenesis by PAH, suggesting that this strain is resistant to phorbol ester tumor promotion. Sencar and C57BL/6 mice seem to respond qualitatively but not quantitatively to one application of TPA. (97 Refs)

53. THE MECHANISM OF THE OXYGEN EFFECT.

Millar BC, Scott OC
Div. Biophysics, Inst. Cancer Res., Clifton Ave., Sutton, Surrey SM2 5PX, England
Stud Biophys; 86(1):15-16 1981

The relationship between oxygen tension and radiation sensitivity in bacterial and mammalian cells is discussed and a more complex model for explaining the effects in two independent sites in the same cell is presented. Computer stimulation suggested that while high oxygen concentration (greater than 7.0 uM) can be fitted to the simpler model, it is not possible to fit the data with low O2 concentrations. Thus, the effect of oxygen in mediating cell death can not be explained by a simple competition model. While DNA single strand breakage may be used as a model for predicting sensitization with electron affinic compounds it cannot be considered a cause of cell death. (5 Refs)

54. CHEMICAL CARCINOGENESIS - THE PRICE FOR DNA-REPAIR?

Wintersberger U
Institut fur Krebsforschung der Universitat, A-1090 Wien, Austria
Naturwissenschaften; 69(3):107-113 1982

This essay examines the possibility of merging the mutation theory of cancer with the hypothesis that cancer is a change in the state of the differentiation of cells. It is suggested that during normal development DNA rearrangements occur, concerning genes which code for differentiation specific cell communication proteins. These proteins are responsible for the proper functioning of growth control in a multi-cellular organism. DNA-damaging agents - mutagens - induced DNA repair enzymes, some of which may catalyze illegitimate genome rearrangements, thus leading to a change of the balance between growth and differentiation. A cell with a selective advantage may arise and become the origin of a tumor. (Author abstract) (77 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. TOXICITY AND METABOLISM OF ACRYLONITRILE.
Sapota A, Chmielnicka J
Zaklad Metabolizmu Substancji Toksycznych, Instytut Medycyny Pracy, ul. Teresy 8, 90-950 Lodz, Poland
Med Pr; 32(1):25-33 1981
In POL

2. A REVIEW OF THE GENOTOXICITY OF FOOD, DRUG AND COSMETIC COLOURS AND OTHER AZO, TRIPHENYLMETHANE AND XANTHENE DYES.
Combes RD, Haveland-Smith RB
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Mutat Res; 98(2):101-248 1982

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BIOLOGICAL ASPECTS OF DNA ALTERATION AND REPAIR IN RELATION TO CARCINOGENICITY

1. NONENZYMATIC METHYLATION OF DNA BY S-ADENOSYLMETHIONINE IN VITRO.

Barrows LR, Magee PN
Fels Res. Inst., Philadelphia, PA, 19140
Carcinogenesis; 3(3):349-351 1982

S-Adenosylmethionine was found to methylate DNA nonenzymatically to produce the same putative promutagenic and procarcinogenic lesions formed by carcinogenic chemical methylating agents. The formation of 7-methylguanine was confirmed by uv spectrophotometry, the formation of O6-methylguanine and 3-methyladenine was suggested by the cochromatography of radioactivity with standard bases. It is possible that this reaction may explain the presence of constitutive cellular enzymes specifically for the repair of methylated DNA, and may indicate the mechanism whereby methylated guanine is formed in the liver DNA of rats with chemically induced liver damage. (Author abstract) (16 Refs)

2. FREQUENCY OF UV-INDUCED NEOPLASTIC TRANSFORMATION OF DIPLOID HUMAN FIBROBLASTS IS HIGHER IN XERODERMA PIGMENTOSUM CELLS THAN IN NORMAL CELLS.

Maher VM, Rowan LA, Silinskas KC, Kateley SA, McCormick JJ
Carcinogenesis Lab., Michigan State Univ., Fee Hall, East Lansing, MI, 48824
Proc Natl Acad Sci USA; 79(8,part1):2613-2617 1982

If neoplastic transformation of diploid human cells results from carcinogen-induced mutations, cells deficient in excision repair of UV-induced DNA damage should be significantly more sensitive to transformation by UV light than normal cells. We tested this hypothesis by irradiating fibroblasts from a xeroderma pigmentosum patient (XP7BE, complementation group D) with low doses of UV light (254 nm) and cells from a normal person with much higher doses and comparing the frequency of transformation to anchorage independence. Both sets of cells exhibited a dose-dependent increase in transformation which corresponded to a dose-dependent decrease in survival. At doses that caused equal cell killing, the frequency of anchorage-independent cells was approximately equal. Colonies of XP7BE and normal cells isolated from agar, propagated, and injected into x-irradiated athymic mice produced fibrosarcomas in 100% of the animals. Normal cells irradiated shortly before the onset of DNA synthesis exhibited a high frequency of anchorage-independent cells; cells irradiated in early G1 showed no increase over background. These results agree with those we observed for UV induction of 6-thio-guanine-resistant mutants in these cells and support the hypothesis that anchorage independence results from mutations induced by DNA replication on a damaged template. (Author abstract) (21 Refs)

3. RELATIONSHIP OF AGE AND STRAIN TO MAMMARY GLAND DNA DAMAGE, REPAIR AND REPLICATION IN VIVO (MEETING ABSTRACT)

Raber JM, Mhaskar DN, D'Ambrosio S
Departments of Pharmacology and Radiology, The Ohio State University, Columbus, OH, 43210
Fed Proc; 41(3):1559 1982

The incidence of mammary gland carcinogenesis depends strongly upon the age and strain of animal. In order to elucidate the underlying mechanisms responsible for these observations, we quantitated: a) the initial levels of alkali sensitive sites induced from a single dose of ENU (ethylnitrosourea) with the use of alkaline sucrose gradient sedimentation in rats both susceptible (Sprague Dawley [SD]) and resistant (Long Evans [LE]) to mammary gland carcinogenesis; b) the fate of such damage in female SD and LE rats at both 30 and 50 days of age; c) the degree of normal gland proliferation in both age groups; and d) the short term effect of ENU on normal mammary gland proliferation. An index of mammary gland proliferation was determined by incorporation of [3H]thymidine into mammary DNA over a two hour time period. Our data showed: a) the initial level of damage induced was higher in the 50 day than the 30 day old rat; b) the alkali labile sites appeared to decrease in both age groups, over the seven day period studied; c) loss of alkali labile sites appeared to be faster in the LE than in the SD rats; and d) normal mammary gland proliferation decreased after a single treatment with ENU. These data relate the induction and persistence of DNA damage (single strand breaks and alkali labile sites) in vivo to mammary gland carcinogenesis as a function of age and strain of rat. (no Refs)

4. IN VITRO INHIBITION OF DNA METHYLASE (DMASE) BY DIRECT CARCINOGENS AND THE PROTECTIVE ABILITY OF THIOL REDUCING AGENTS (MEETING ABSTRACT)

Chan JY, Ruchirawat M, Lapeyre JN, Becker FF
M. D. Anderson Hospital and Tumor Institute, Houston, TX, 77030
Fed Proc; 41(3):685 1982

The role of DNA methylation during carcinogenesis is unknown although DNA from carcinogen-treated rat liver is hypomethylated. To determine if carcinogens directly affect DMase, the direct-acting carcinogens acetoxyacetylaminofluorene (AcAAF) and methylnitrosourea (MNU) were tested in vitro on DMase activity from rat liver. Fifty percent inhibition of DMase activity was achieved with 4.3 mM AcAAF and 47 mM MNU. The sensitivity of DMase towards direct carcinogens was similar to that for DNA polymerase-alpha, while DNA polymerase-beta, the putative repair enzyme, was highly resistant to carcinogen damage. When various thiol reducing agents were tested for their ability to protect DMase from carcinogen damage, differential protective ability was observed. Dithiothreitol, beta-mercaptoethanol and reduced glutathione were effective in protecting DMase from AcAAF damage while the effects of cysteine and ergothioneine were small. At 10 mM of these agents, the percent of DMase activity recovered after interaction with 6.7 mM of AcAAF was 94,86,78,34 and 12, respectively. These effects may have some bearing on the DNA hypomethylation observed in vivo, suggesting that the carcinogens tested may achieve their inhibitory effect by affecting crucial thiol(s). These data also suggest that various intracellular thiols may play an important role in protecting DNA modifying enzymes from carcinogen damage. (no Refs)

5. INDUCTION OF UNSCHEDULED DNA SYNTHESIS IN RAT HEPATOCYTES FOLLOWING IN VIVO TREATMENT WITH DINITROTOLUENE.

Mirsalis JC, Butterworth BE
SRI International, Building 205, 333 Ravenswood Ave., Menlo Park, CA, 94025
Carcinogenesis; 3(3):241-245 1982

The purpose of this study was to examine the induction of unscheduled DNA synthesis (UDS) by the potent hepatocarcinogen technical grade dinitrotoluene (tgDNT; 76% 2,4-dinitrotolulene, 19% 2,6-dinitrotolulene) using the in vivo-in vitro hepatocyte DNA repair assay. Male Fischer-344 rats were treated by gavage and hepatocytes were isolated by liver perfusion and cultured with [3H]thymidine. UDS was measured by quantitative autoradiography as net grains/nucleus (NG); greater than or equal to NG was considered positive. Controls consistently had-3 to-6 NG. A dose-related increase in UDS was observed 12 hr after treatment, with 200 mg/kg tgDNT producing 26 NG. A 50-fold increase in the number of cells in S-phase was observed at 48 hr after treatment. This increase in S-phase cells could be suppressed in the presence of 10-20 mM hydroxyurea (HU), while the same levels of HU did not affect the level of UDS at 12 hr after treatment. 2,4-DNT produced only a weak response, in contrast to 2,6-DNT which was a potent inducer of UDS. Treatment of female rats with tgDNT yielded only modest increases in UDS and DNA replication relative to males. These results are consistent with the carcinogenicity studies and indicate that tgDNT is a potent genotoxic agent, with 2,6-DNT contributing the major portion of the effect. (Author abstract) (20 Refs)

BIOLOGICAL ASPECTS OF DNA ALTERATION AND REPAIR IN RELATION TO MUTAGENICITY

6. SELECTIVE ALKYLATION OF NUCLEIC ACIDS BY CARCINOGENS MAY CAUSE MISCODING IN DNA. A THEORETICAL STUDY.

Klopman G, Ray A
Case Western Reserve Univ., Cleveland, OH, 44106
Cancer Biochem Biophys; 6(1):31-35 1982

The CNDO/II method was used to study the pairing abilities of various alkylated nucleic acids. On the basis of these results, a mechanism for mutation (carcinogenesis) is proposed. Our calculations suggest that O-(6) alkylated guanine and/or O-(4) alkylated thymine could cause miscoding during the replication of DNA. (Author abstract) (26 Refs)

7. MODERN DEVELOPMENTS IN MUTAGENESIS.

Saunders G, Allsop A, Holt G
Sch. Engineering and Science, Polytechnic Central London, 115 New Cavendish St., London W1M 8JS, England
J Chem Technol Biotechnol; 32(1):354-364 1982

The increase in mutation yield was studied in Penicillium chrysogenum and Streptomyces clavuligerus. Five mutants of S clavuligerus and one of P chrysogenum were isolated on the basis of increased sensitivity to far UV light (FUV). The sensitivities of these mutants and other mutagens are presented. The mutation rates of these strains in response to a range of mutagens were estimated by various forward mutation systems, including mutation to acriflavine, rimfampicin, ethidium bromide, or 5-fluorouracil resistance and 2-thioxanthine non-utilization. The mutational responses of the UV sensitive (UVs) strains and their parents are illustrated. No differences were detected in P chrysogenum between the UVs-strain and its parent in induced mutation frequency after FUV or ethylmethanesulphonate treatment. A significant difference was observed after gamma-irradiation where the UV-strain showed a reduced mutational yield relative to its parent. All five strains of S clavuligerus were altered in mutational response to FUV. In wild-type strains of S clavuligerus caffeine (CF) increased FUV mutation and decreased survival after irradiation. Unlike S clavuligerus where CF was added after irradiation, the spores of P chrysogenum had to be pretreated in CF soln prior to irradiation. CF increased the induced-mutation frequency of the UVs strains and its parent, the effect being greatest in the UVs strain. CF led to higher survival levels in the sensitive strain and decreased survival in its parent. Processes such as liquid holding and nalidixic acid treatment, which have been shown to affect DNA replication, caused an increase in FUV-induced mutation in P chrysogenum. A similar effect on mutation frequency was observed in S clavuligerus when spores were liquid held. (54 Refs)

8. AZASERINE: SURVIVAL AND MUTATION IN ESCHERICHIA COLI.

Kubitschek HE, Sepanski RJ
Div. Biological and Medical Res., Argonne Natl. Lab., Argonne, IL, 60439
Mutat Res; 94(1):31-38 1982

The nature of the genetic and molecular mechanisms involved in the lethal and mutagenic effects of azaserine (AZS) were investigated in Escherichia coli strain WP2 and a series of its repair-deficient mutants. Survival of cells removed from stationary-phase cultures at 18, 41, 65, and 180 hr after inoculation into minimal medium and exposure to various concentrations of AZS was biphasic with the initial and final slopes differing by approx two orders of magnitude. The magnitude of the more resistant cell fraction was strongly dependent upon the age of the culture and could be further increased with growth in nutrient broth. In 18-23 hr cultures in minimal medium, strain WP2 showed the most resistance to AZS, and the mutants deficient in only one repair function were increasingly sensitive in the order WP10, WP2s, WP5, and WP6. The doubly repair-deficient mutant strains WP100 and Bs-1 had the greatest sensitivities. When cultured on nutrient agar, the order of sensitivities of WP2 and WP10 were reversed. Under both culture conditions, the wild type strain was about 8x as resistant to AZS as was the most sensitive repair-deficient mutant. These results suggest that exposure to AZS produces lethal DNA lesions. Mutation frequencies in the excision-defective strain were about 60x those in the wild-type strain WP2, and mutation frequencies in strain WP6 were about 3x those in the wild-type strain. Induced mutation was not observed in strain WP5 or WP10. AZS appears to react with DNA in vivo, either directly or indirectly, producing lesions capable of causing cell death unless repaired. Mutagenesis occurs by misrepair in the SOS repair system. (18 Refs)

9. PHOTODYNAMIC EFFECTS OF DYES ON BACTERIA. V. MUTAGENESIS BY ACRIDINE ORANGE AND 46-NM OR 500-NM LIGHT IN STRAINS OF ESCHERICHIA COLI THAT DIFFER IN REPAIR CAPABILITY.

Hass BS, Webb RB
Shell Development Co., Westhollow Res. Center, Box 822, Houston, TX, 77001
Mutat Res; 94(1):39-51 1982

The effect of acridine orange (AO) and 460 nanometer (nm)- or 500-nm light on mutagenesis in strains of Escherichia coli differing in repair capabilities was investigated. It had been previously shown that AO is a weak to moderate dark mutagen in all strains tested except for the wild-type strain WP2. When irradiated with 460 nm light, in the presence of AO WP2s showed a mutation rate significantly lower than wild-type. Results comparing the effects of 460 nm light to 500 nm light suggest that the uvrA+(endonuclease) gene product does not effectively contribute to the repair of the lesions produced by AO and 460 nm light. DNA lesions responsible for mutation induction in strains WP10, WP6, and Bs-1 by AO and 460 nm light are different from those produced by AO and 500 nm light. Endonuclease repair can affect the mutagenic response to AO in the dark. DNA lesions induced by AO and 500 nm light are not effectively repaired by the uvrA endonuclease, and the effect of the absence of the uvrA endonuclease was even greater with externally bound AO. With 460 nm light, the mutation rate in the uvrA strain WP2s was 0.31 of the value of the wild-type strain WP2. Thus the absence of the uvrA endonuclease increased the dark AO mutation rate, but decreased the photodynamic mutation rate obtained with AO plus light at either wavelength. It appears that uvrA strains may be inadequate for identifying some classes of mutagens. The relatively high rates of mutation in the wild-type and polA strains tested suggest that such strains should be included in mutagen screening programs. (26 Refs)

10. VARIATIONS AMONG SPECIES AND CELL TYPES IN THE EFFECTS OF CAFFEINE ON MUTAGEN-INDUCED CYTOTOXICITY AND POSTREPLICATION REPAIR OF DNA.

Sivak A, Rudenko L, Teague LG
Arthur D. Little, Inc., Cambridge, MA, 02140
Environ Mutagen; 4(2):143-162 1982

Caffeine effects in culture of rodent and human cells are reviewed, and the effects of caffeine on postreplication repair induced by chemical mutagens in normal human fibroblasts (HS-WP), human xeroderma pigmentosum fibroblasts (SGL), mouse BALB/c-3T3 fibroblasts, Syrian hamster embryo cells (SHE), and Chinese hamster V79 cells are reported. Cells were exposed to UV light (100 ergs/square mm), nitroquinoline-N-oxide (NQO: 2.5 uM), N-acetoxy-N-2-fluorenylacetamide (AFFA: 2.0 uM), and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG: 50.0 uM) and then to caffeine (0.05-1.0 milliM). Cytotoxicity was enhanced by addition of caffeine to V79 cells and BALB/c-3T3 cells after exposure to either UV light or AFAA. Postreplication repair of V79 cells was inhibited in cells exposed to UV and AFFA. Postreplication repair was not affected by caffeine at concentrations up to 1.0 milliM in HS-WP, SGL, SHE and mouse BALB/c-3T3 cells after exposure to UV, AFAA, NQO, or MNNG. Repair in BALB/c-3T3 cells exposed to UV or AFAA was also unaffected. The failure of cytoxicity results to agree with repair results for most of these cells indicates that it is incorrect to use cytotoxicity evidence for caffeine to imply that genetic damage has occurred. (49 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN VERTEBRATES

11. EFFECT OF AFLATOXIN B1 ON THE REPAIR OF O6-METHYLGUANINE IN THE HEPATIC DNA OF RATS AND MICE (MEETING ABSTRACT)

Maru GB, Margison GP, Chu YH, O'Connor PJ
Christie Hospital, Manchester, England
Br J Cancer; 44(2):273 1981

Pretreatment of male Wistar rats by ip injection of single (2 mg/kg) or multiple (4x0.5 mg/kg) doses of aflatoxin B1 (AFB) stimulates the process for the removal of O6-methylguanine from hepatic DNA in animals challenged with a single dose (2 mg/kg) of [14C]-dimethylnitrosamine (DMN). The sensitivity of this system in terms of its ability to 'adapt', is indicated by the fact that the repair response can be detected as early as one day after pretreatment with a single dose. However, treatment of mice (C57Bl, males) with doses from 0.1 to 100 mg/kg of AFB, had no marked effect on the activity of the O6-meG repair system, when assayed in vitro using cell-free liver extracts and DNA methylated with [3H]-MNU as substrate. This murine repair system has been titrated in vivo, using a range of doses of [14C]-DMN (0.25-10 mg/kg). In terms of saturation kinetics it appears to be intermediate between the Syrian golden hamster and the rat but more closely resembling that for the rat. Different doses of AFB and exposure periods are under investigation, but it is tentatively concluded that the mouse, like the hamster and in contrast to the rat, is refractory to the inducibility of the O6-meG repair system. (3 Refs)

12. DNA DAMAGE, REPAIR AND DMBA METABOLISM IN HUMAN FETAL CELLS (MEETING ABSTRACT)

D'Ambrosio SM, Gibson-D'Ambrosio RE, Oravec C, Leong Y, Chang D
Departments of Pharmacology and Radiology, College of Medicine, The Ohio State University, Columbus, OH, 43210
Fed Proc; 41(3):1559 1982

The level of DNA damage, repair and replication following UV irradiation and N-ethyl-N-nitrosourea (ENU) treatment as well as the binding and metabolism of 7,12-dimethylbenz(a)anthracene (DMBA) was quantitated and compared in vitro in cells derived from human fetal brain, dermis, kidney, liver, intestine and lung. Using UDS (unscheduled DNA synthesis) as a measurement of DNA repair, fetal brain, kidney and liver cells exhibited lower (30-60%) levels of UDS than did fetal dermal, lung or intestinal cells treated with UV radiation or ENU. The order for repair of UV induced DNA damage was: dermal greater than lung greater than intestinal greater than kidney greater than liver greater than brain cells. The order for UDS following ENU treatment was: lung greater than dermal greater than intestinal greater than brain greater than liver cells. Intestinal cells metabolized DMBA approximately 30%, while brain cells metabolized only 2.6% of the DMBA. Liver, dermal, lung and kidney, metabolized 5-10% of the DMBA during a 48 hour period. Using HPLC (high pressure liquid chromatography), qualitative as well as quantitative differences in the metabolite profiles were observed in each cell culture. The level of DMBA binding to cellular DNA was of the order: intestinal greater than lung greater than liver greater than dermal greater than kidney cells. These studies provide, important information as to how various human fetal organs metabolize DMBA, repair DNA damage and replicate new DNA following carcinogen exposure. (no Refs)

13. DNA REPAIR AND REPLICATION IN MOUSE AND HUMAN LYMPHOCYTES FOLLOWING TREATMENT WITH DNA DAMAGING AGENTS (MEETING ABSTRACT)

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Fed Proc; 41(3):1558 1982

The extent of DNA repair and replication was measured and compared in mouse spleen (MS) and human peripheral blood mononuclear cells (HPBMC) following in vivo (MS) and/or in vitro (MS and HPBMC) treatment with N-ethyl-N-nitrosourea (ENU), bleomycin (BLM) and/or ultraviolet radiation (UV). Both ENU and UV induced UDS in MC and HPBMC in culture. The ENU damage induced in MS in vivo appeared to be lost 24 hr post-treatment, since very low levels of UDS were observed compared to 1 hr post-injection. The level of UDS following a combination of ENU and UV were lower in HPBMC (50%) and MS (30%) treated in culture. ENU also inhibited 30% of the scheduled DNA synthesis (SDS) observed in HPBMC. BLM required the presence of the rat liver microsomes activation system for induction of UDS, but not for inhibition of SDS in MS and HPBMC in culture. BLM however did not appear to induce UDS in MS from mice treated in vivo, although it appeared to inhibit (50%) UDS following UV irradiation of MS cells. These data compares the differences and similarities between different types of DNA damaging agents given in vitro and in vivo and in mouse and human lymphocytes. (no Refs)

14. DNA ADDUCT FORMATION IN HUMAN AND RAT PANCREATIC EXPLANTS TREATED WITH N-METHYL-N-NITROSOUREA (MNU) (MEETING ABSTRACT)

Friedman S, Parsa I
State University of New York, Downstate Medical Center, Brooklyn, NY, 11203
Fed Proc; 41(3):1548 1982

To evaluate the carcinogenic process in an in vitro model of pancreatic carcinogenesis the early effects of carcinogens on pancreatic explants in organ culture were studied. We have reported that adult human pancreatic explants can be transformed in organ culture by treatment with MNU. Since adduct formation of carcinogens with DNA is believed to play a role in carcinogenesis and is a measure of the reactivity of carcinogens with cellular macromolecules we have examined the reaction products of this alkylating agent with DNA under conditions, in organ culture, which cause the transformation of human pancreatic explants. Explants were exposed to 14C-MNU for 2 hours in a chemically defined medium. Total DNA was extracted by a modification of the method of Marmur and the purines analyzed after hydrolysis of the DNA in 0.1 M HCl at 70 degrees for 30 min by chromatography on Sephadex G-10. The analysis of methylated purine bases formed in the DNA of human pancreas indicates the formation of 1-methyladenine (0.0045 bases/1000 parent base), 3-methyladenine (0.0210), 7-methyladenine (0.0093), 7-methylguanine (0.239) and 06-methylguanine (0.024). MNU is approximately 1/10 as active in alkylating DNA of rat pancreatic explants as it is in alkylating DNA of human pancreas. (no Refs)

15. PHOTOPROMOTION OF SISTER CHROMATID EXCHANGES BY PSORALEN DERIVATIVES.

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Arch Dermatol Res; 272(3/4):239-244 1982

Human peripheral blood WBC exposed to UV in combination with 8-methoxypsoralen (8-MOP), 8-MOP derivatives, or 4,5'-trimethylpsoralen (TMP) derivatives were scored for sister chromatid exchanges (SCE). Flasks containing cells cultured for 24 hr were exposed to psoralen concentrations of 6.5 x 10(-8) M and UV-A irradiation (365 nanom, 0.9 Joules/cm(2)). Control cultures showed 16.5 SCE/100 chromosomes. 8-MOP was the least active SCE promoter (23.9 SCE/100 chromosomes), followed by 5'-methyl 8-methoxylpsoralen (25.7), 4-methyl-8-methoxypsoralen (27.8), and 4,5'-dimethyl-8-methoxypsoralen (31.9). TMP derivatives 4'-methoxymethyl-4,5'8-trimethylpsoralen, 4'aminomethyl-4,5'8-trimethylpsoralen-HC1, and 4'hydroxymethyl-4,5'8-trimethylpsoralen were the most active promoters (42.9, 59.1, and 75.0 SCE/100 chromosomes, respectively). Relative water insolubility, DNA binding affinity, and cross-linking ability were correlated with ability to promote SCE. (18 Refs)

16. STRUCTURAL CHANGES IN MAMMALIAN CELL DNA INDUCED BY LOW-DOSE X-RAY DAMAGE AND SUBSEQUENT POSTIRRADIATION INCUBATION IN THE PRESENCE AND ABSENCE OF CAFFEINE.

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Radiat Res; 90(2):310-320 1982

Experiments on low-dose (30-2,000 rad) x-ray-induced damage in rat 9L cells in vitro and subsequent posttreatment irradiation measured under neutral (pH 7) conditions are described. Results indicated that the principal retardation time of DNA in neutral lysates was sensitive to x-irradiation of the cells. The retardation time increased by about a factor of seven in the dose range of 0-1,000 rad, the major portion of the increase occurring with the first 300 rad. The biphasic nature of the response to increasing doses of radiation appeared to be unique to the viscoelastic method utilized. The viscoelastic retardation time showed a complicated pattern reflecting different structures of DNA during postirradiation incubation. No indication of loss of large DNA during postirradiation incubation was observed. Results were interpreted as suggesting conformational changes in damaged DNA during repair. Post-irradiation incubation in the presence of 0.5 milliM caffeine resulted in inhibition of DNA repair. (29 Refs)

17. THE INHIBITION OF DNA REPAIR BY APHIDICOLIN OR CYTOSINE ARABINOSIDE IN X-IRRADIATED NORMAL AND XERODERMA PIGMENTOSUM FIBROBLASTS.

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Mutat Res; 94(1):229-234 1982

By incubating x-irradiated human fibroblasts with or without aphidicolin (APC) or cytosine arabinoside (AraC), it was investigated (1) whether DNA polymerase alpha participates in the repair of x-ray-induced DNA damage in normal and xeroderma pigmentosum (XP) cells incapable of excising UV-in-

duced pyrimidine dimers, and (2) whether any responses seen with APC are observed with AraC, a known inhibitor of DNA replication and DNA repair in mammalian cells. Normal fibroblasts and excision-deficient XP fibroblasts were prelabeled with [14C]- and [H3]thymidine, respectively, They were then plated in the same dishes and exposed to a range of x-ray doses prior to incubation with or without either APC or AraC. DNA was then isolated on alkaline sucrose gradients. Profiles of gradients indicated that after doses of 150 or 250 Grays the repair of a fraction of the DNA damage was inhibited in both normal and XP cells by APC or AraC. Incubations with both AraC and APC did not increase the breaks seen with either agent alone. The response to post-irradiation incubation with APC was very similar to that seen with AraC, which was also seen after UV-irradiation. It was suggested that AraC blocks both semi-conservative replication and repair replication in a way similar to that of APC, ie, by blocking DNA polymerase alpha. (12 Refs)

18. ENHANCED RADIOSENSITIVITY AND DEFECTIVE DNA REPAIR IN CULTURED FIBROBLASTS DERIVED FROM ROTHMUND THOMSON SYNDROME PATIENTS.

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Mutat Res; 94(1):213-228 1982

Colony forming ability and DNA repair capacity was measured in cultured fibroblasts from four patients with Rothmund Thomson syndrome (RTS). RTS is an oculocutaneous disorder showing autosomal recessive inheritance. All reported cases have been in caucasians, 70% in females. Ancestry of patients can often be traced to the Swiss or Austrian Alpine areas. The normal strains GM38, GM498 and 265OT was used as parallel controls for the RTS strains. Compared to the normal fibroblast strains, 2/4 RTS strains showed significantly enhanced sensitivity to ionizing radiation delivered under hypoxic conditions. Strain RT1MO also showed enhanced sensitivity when irradiated in air whereas strain RT1SE did not. Hypoxic gamma-ray sensitivity was accompanied by the inefficient removal of a class of DNA damage sensitive to incising activities present in a protein extract of Micrococcus luteus. Defective DNA repair in RTS was confirmed by the detection of reduced levels of repair synthesis. Because the present study was restricted to the gamma-ray responses of RTS strains, it is possible that RTS strains that responded normally to gamma-rays may show defective repair of other carcinogen-induced DNA lesions. (32 Refs)

19. POLY(ADENOSINEDIPHOSPHORIBOSE) POLYMERASE INHIBITORS STIMULATE UNSCHEDULED DEOXYRIBONUCLEIC ACID SYNTHESIS IN NORMAL HUMAN LYMPHOCYTES.

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Biochemistry; 21(8):1813-1821 1982

Thirty-three analogues of the nicotinamide and adenine portions of NAD+ were evaluated for (1) their effectiveness as inhibitors of poly(adenosinediphosphoribose) polymerase in nucleotide permeable lymphocytes, (2) their ability to interfere with NAD+ lowering in DNA-damaged cells, (3) their ability to inhibit accumulation of poly(adenosinediphosphoribose) in DNA-damaged cells, and (4) their ability to stimulate unscheduled DNA synthesis in DNA-damaged cells. Poly(adenosinediphosphoribose) polymerase was effectively inhibited by six-membered aromatic ring compounds containing a carboxamide group such as nicotinamide, picolinamide, 5-methylnicotinamide, benzamide, 3-aminobenzamide, and 5-methoxybenzamide. Compounds containing a carboxylic acid group rather than a carboxamide group did not inhibit poly(adenosinediphosphoribose) polymerase. Purine analogues such as theobromine and theophylline were also effective inhibitors of poly(adenosinediphosphoribose) polymerase. The ability of these compounds to inhibit poly(adenosinediphosphoribose) polymerase in nucleotide permeable cells correlated with their ability to retard NAD+ lowering in vivo in cells treated with N-methyl-N'-nitro-N-nitrosoguanidine. However, the most effective polymerase inhibitors caused the greatest retardation in the rate of NAD+ lowering. The compounds that were the most effective polymerase inhibitors in vitro were also the most potent in retarding NAD+ lowering in vivo and the most potent in delaying poly(adenosinediphosphoribose) accumulation in vivo. These compounds were also found to be the most effective stimulators of unscheduled DNA synthesis. For example, unscheduled DNA synthesis in UV-irradiated cells was stimulated two-fold by treatment with 2 mM benzamide, nicotinamide, or 3-aminobenzamide. (24 Refs)

20. STUDY OF THE MOLECULAR MECHANISMS OF RADIATION DEATH OF LYMPHOID CELLS. COMMUNICATION 2. DAMAGE AND REPAIR OF SUPERHELICAL DNA IN THYMOCYTES OF MICE SUBJECTED TO GAMMA-IRRADIATION.

Soldatenkov VA, Sorokina NI, Filippovich IV, Romantsev EF
No affiliation given
Radiobiologiia; 22(1):25-30 1982

The repair of superhelical DNA was studied in a culture of thymocytes from (CBA x C57BL)F1 male mice irradiated with gamma rays. Sedimentation analysis of nucleotide motility showed that irradiation of of thymocyte suspension produced a dose-dependent relaxation of the superhelical DNA domains. Incubation of irradiated cells at 37 C resulted in repair of single-stranded breaks in superhelical DNA. (18 Refs) (In RUS)

DNA ALTERATION AND REPAIR MECHANISMS IN INVERTEBRATES AND LOWER EUKARYOTES

21. GENETIC DAMAGE INDUCED BY X-RAYS OR NEUTRONS IN SPERMATOZOA OF DROSOPHILA MELANOGASTER; DIFFERENTIAL PROCESSING IN THE OOCYTES OF FEMALES CARRYING THE DNA-REPAIR-DEFICIENT MUTANTS MEI-9A AND MUS-101D1.

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Mutat Res; 94(1):63-78 1982

Two DNA-repair-deficient mutants of Drosophila melanogaster, mei-9a and mus-101D1, were used to assay the specific types of DNA lesions that might be produced by specific types of irradiation, in this case x-rays vs neutrons. Irradiated Basc males were crossed to homozygous mei-9a or mus-101D1 fe-

males, or to repair-proficient control females. Frequencies of recovered sex-linked recessive lethal mutations and of II-III translocations were used to assess the effects of impaired maternal repair. From irradiated Basc males crossed to mei+ and mus+ control females, sex-linked recessive lethals were recovered at a frequency of 4.05% after x-ray treatment, against 6.44% after exposure to neutrons [relative biological effectiveness (RBE) = 1.64]. Basc males crossed to mei-9a females gave lethal frequencies of 6.32% with x-rays, 5.58% with neutrons, and 1.46% spontaneous lethals (RBE = 0.85). Neutron lesions appeared to end up as recessive lethals at a lower frequency in zygotes derived from fertilized eggs of mei-9a females in comparison with control zygotes from mei+mus+ females. Both types of radiation led to a much reduced recovery of translocation when mus-101D1 females were used; with x-rays, the induction frequency was only 1.24%, or less than half the frequency of 2.93% observed with mei+mus+ controls. With neutrons, a slightly higher value of 1.60% was observed. The pattern of effects brought about by the two mutants was different. Not only could mus-101D1 be distinguished from mei-9a by its stonger effects on the recovery of neutron-induced damage, but it also showed an end-point specific effect on translocation recovery in the x-ray experiments. (44 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN BACTERIA

22. RESISTANCE OF SALMONELLA TYPHIMURIUM TA 1535 TO O(6)-GUANINE METHYLATION AND MUTAGENESIS INDUCED BY LOW DOSES OF N-METHYL-N'-NITRO-N-NITROSOGUANIDINE: AN APPARENT CONSTITUTIVE REPAIR ACTIVITY.

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Carcinogenesis; 3(3):327-331 1982

Salmonella tester strains which are reverted by base-pair substitution mutagens are relatively insensitive to the mutagenic effects of N-methyl-N-nitroso compounds. One reason for this insensitivity is the ability of these strains to withstand low doses of these compounds before they become sensitive to their mutagenic effects. In this report it is shown that mutagenesis induced by treatment of Salmonella typhimurium TA 1535 with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) in buffer is biphasic with a low sensitivity range at low doses where little mutagenesis occurs, followed by a high sensitivity range whose onset begins after an apparent threshold dose has been exceeded. Levels of O6-methylguanine (O6-MeG) in the DNA extracted from the bacteria follow a similar dose-response curve suggesting a dependency of mutagenesis on O6-MeG. In contrast, levels of 7-methylguanine (7-MeG) in the DNA increase linearly with dose. O6-MeG was undetectable at the lowest dose of MNNG whereas 7-MeG was readily detectable. Although such resistance to O6-alkylation has been demonstrated in MNNG-pretreated (adapted) E coli, it has not been reported in unpretreated cells. When isolated DNA was treated with MNNG a linear dose-response in the generation of O6-MeG was observed. The lack of O6-MeG in DNA isolated from MNNG treated cells after low doses is attributed to a saturable, constitutive repair activity in the bacteria. An attempt to observe the removal of O6-MeG from the bacteria after exposure to a short challenge dose of N-nitroso-N-methylurea (NMU) followed by a subsequent incubation in buffer was unsuccessful, probably because all the repair occurred within the time necessary to treat and lyse the cells. (Author abstract) (22 Refs)

23. ADAPTATION TO ALKYLATION RESISTANCE INVOLVES THE INDUCTION OF A DNA GLYCOSYLASE.

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Nature; 296(5859):773-775 1982

The possibility of two pathways for repair of 3-methyladenine residues in Escherichia coli DNA was examined. The first pathway appears to be consitutively expressed and controlled by the gene tag, the second inducible and controlled by ada. Adaptive treatment with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), used to induce 6-methylguanine DNA methyltransferase, also induced high levels of 3-methyladenine DNA glycosylase activity in the tag mutant (BK2114). This induction was not seen in the tag ada double mutant (BK2106). BK2114 additionally regained its ability to reactivate alkylated phages. These results indicate the induction of two separate enzymes for repair of alkylated DNA: 6-methylguanine DNA methyltransferase and 3-methyladenine DNA glycosylase. Both of these enzymes appear under ada control. Since the ada mutation prevents induction of these two separate repair enzymes, the ada gene may be a control gene for the adaptive response. Structural genes for one or both enzymes may be situated elsewhere on the chromosome. Another mutant, alk-1, was found deficient in the induction of TagII but proficient in induction of the methyltransferase. 6-Methylguanine DNA methyltransferase is thought responsible for mutagenic adaptation, while ada+-dependent inducible glycosylase may be responsible for killing adaptation, because DNA polymerase I is required to complete repair of the apurinic site formed by glycosylase action. (14 Refs)

24. FURTHER STUDIES ON THE CO-TRANSFORMATION OF DISTANT MARKERS FOLLOWING THE EXPOSURE OF DNA TO CARCINOGENS INCLUDING CARCINOGENIC METALS (MEETING ABSTRACT)

Kubinski H, Kubinski ZO
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Fed Proc; 41(3):685 1982

Exposure of Bacillus subtilis transforming DNA to chemical carcinogens produced a decrease in transforming activity of such DNA and a decrease in co-transformation of linked markers (tyr-trp). Under carefully controlled conditions an increase in co-transformation of distant (unlinked) markers (tyr-leu and trp-leu) was detected, indicating the formation of DNA-DNA complexes capable of penetrating into the interiors of the recipient cells. However, based on our studies of N-acetoxy-2-acetylaminofluorene - treated DNA, up to 80% of these complexes were eventually 'repaired', restoring the original chromosomal locations of these unlinked markers. Occasionally, the artificially linked pieces of DNA were inserted into adjacent loci in the recipients cell's chromosome. In separate studies, effects of various salts of chromium on the transforming DNA were investigated. An increased co-transformation of the unlinked markers was observed with Cr VI but not with Cr II or Cr III. The former, but not the latter are believed to produce tumors in humans. Thus, these observations support our earlier suggestion that only those mutational events which produce macromolecular complexes may be responsible for the malignant transformation in vivo. (no Refs)

25. PHOTOPRODUCT FORMATION AND REPAIR CAPACITY IN A MUTANT OF BACILLUS CEREUS 569 PRODUCING UV-SENSITIVE SPORES.

Weinberger S, Evenchik Z, Hertman I
Israel Inst. Biological Res., Ness Ziona, Israel
Mutat Res; 94(1):1-12 1982

The isolation of N-methyl-N'-nitro-N-nitroso-guanidine-induced mutants of Bacillus cereus 569 sensitive to UV in both vegetative and sporal stages is reported. In this mutant (2422) a single mutation in a gene coding for a step in excision repair apparently leads to the observed sensitivity of both cells and spores. Dipicolinic acid content of spores of strain 2422 was similar to that of wild type, indicating that the mutation induced was not involved in the synthesis of this product. For a given UV dose, both the mutant 2422 and the wild type formed the same types and the same amount of photoproducts. The dominant photoproduct for vegetative cells was cyclobutane-thymine dimers, and for spores 5-thyminyl-5,6-dihydrothymine (TDHT). Under conditions permitting germination but no outgrowth, only about 50% of TDHT lesions were removed; no significant difference was observed in rates of removal in the wild type vs the mutant strain. Under growing conditions only the wild-type 569 improved in rate of removal of TDHT. These findings suggest more than one pathway for TDHT removal. Under growing conditions plus energy source, the wild type 569 excised approx 75% of initial thymine dimers, compared to only 26% in the mutant. Reversion analysis indicated that UV resistance was regained by single gene mutation. This gene is apparently involved in the removal of bases or nucleotides, and plays a major role in the repair of UV-induced damage in both spores and vegetative cells. (29 Refs)

MACROMOLECULAR BINDING OF CARCINOGENS

26. DISTRIBUTION OF BENZO(A)PYRENE-DNA ADDUCTS WITHIN MAMMALIAN CHROMATIN (MEETING ABSTRACT)

Jack PL, Brookes P
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Br J Cancer; 44(2):274 1981

The distribution of benzo(a)pyrene (BP)-DNA adducts within mammalian cell chromatin was examined by micrococcal nuclease digestion of nuclei from carcinogen-treated cells. Friend erythroleukemia cells, prelabelled with [14C]-dT (deoxythymidine), were treated with 3H-benzo(a)pyrene-7,8-diol-9,10-epoxide (BPDE) and a nuclear fraction prepared. Micrococcal-nuclease digestion of nuclei, harvested immediately after treatment, indicated a 4-fold enrichment of BP-DNA adducts on the linker region between nucleosome cores. Analysis of DNA, isolated from briefly digested nuclei by agarose gel electrophoresis, indicated that mononucleosomes released early during digestion contained slightly more adducts than total DNA. Treatment of primary mouse embryo cells with BPDE showed a similar enrichment of BP-DNA adducts within the linker region, however treatment of such cells with BP for 72 hr (necessary to allow metabolic activation) showed no such preferential location. This apparent difference between the 2 agents was resolved by showing that post-treatment incubation of BPDE-treated cells led to a loss of the preferential linker binding. The time-dependent loss of preferential binding was shown to be independent of DNA replication, since it also occurred when hydroxyurea, an inhibitor of DNA synthesis, was present during post-treatment incubation of the confluent cultures. (no Refs)

27. MECHANISM FOR THE LOSS OF PREFERENTIAL BENZO[A]PYRENE BINDING TO THE LINKER DNA OF CHROMATIN.

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Carcinogenesis; 3(3):341-344 1982

We have examined the fate of the asymmetric chromosomal distribution of DNA adducts generated by the chemical carcinogen r-7,t-8-dihydroxy-t-9,10-oxy-7,8,9,10 tetrahydrobenzo[a]pyrene (BPDE). Treatment of mouse embryo cells with BPDE results in 3.5x more binding to the linker DNA regions between nucleosome cores than to the nucleosome core DNA itself, but 24 hr post-treatment incubation of these cells leads to a loss of this non-random binding. A similar result was obtained when post-treatment incubation was carried out in the presence of hydroxyurea indicating that factors other than DNA replication are responsible for this change in adduct distribution. However in the case of excision repair deficient xeroderma pigmentosum (XP12/BE) cells the non-random adduct distribution was stable over a period of 48 hr, whereas with excision repair proficient XP variant (XP4/BE) cells, loss of preferential binding did occur. These results indicate that the loss of non-random nucleosomal DNA modification with time can be accounted for by the preferential removal of adducts from micrococcal nuclease sensitive linker DNA and further, demonstrates that in certain cells at least, the relative position of nucleosome core structures on DNA remains unchanged over a period of at least 48 hr. (Author abstract) (18 Refs)

28. INTERCALATIVE BINDING OF 3-NITROBENZOTHIAZOLO (3,2-A) QUINOLINIUM SALT TO DNA (MEETING ABSTRACT)

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Fed Proc; 41(3):1202 1982

NBQ (3-Nitrobenzothiazolo (3,2-a) quinolinium perchlorate) has been shown previously to exert strong cytostatic and antitumor activity. The deoxyribonucleic acid (DNA) binding characteristics of NBQ have been studied by UV-visible and fluorescence spectrophotometric, thermal denaturation and viscometric methods. Viscometric studies showed that NBQ increased the viscosity of sonicated rod-like DNA fragments. Binding parameters were determined by spectrophotometric studies. The results obtained are consistent with an intercalative binding model for the NBQ DNA interaction. (no Refs)

29. PHYSICAL BINDING OF DIOL-EPOXIDE DERIVATIVES OF THE CARCINOGEN BENZO(A)PYRENE TO DNA (MEETING ABSTRACT)

MacLeod MC, Selkirk JK
Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN, 37830
Fed Proc; 41(3):685 1982

Two metabolically-formed, diol-epoxide derivatives of the strong carcinogen benzo(a)pyrene [B(a)P], 7,8-dihydroxy-9,10-oxy-7,8,9,10-tetrahydro benzo(a)pyrene (BPDE) and 9,10-dihydroxy-7,8-oxy-7,8,9,10-tetrahydro benzo(a)pyrene (reverse-BPDE), have been implicated in covalent binding to nuclear proteins in hamster embryo cells treated for 24 hr with B(a)P. However, only BPDE binds to DNA in treated cells. We have used the characteristic bathochromic shift in the absorbance spectra of polycyclic aromatic hydrocarbon DNA intercalation complexes to probe the in vitro physical interactions of BPDE and reverse BPDE with purified DNA. Both diol epoxides form intercalation complexes with similar association constants and intercalation is blocked by low concentrations of Mg++. In addition, the rate of hydrolysis of BPDE and to a lesser extent of reverse BPDE, is enhanced by DNA. This enhancement of hydrolysis is blocked by low concentrations of Mg++ suggesting the involvement of intercalation complexes in the mechanism of enhanced hydrolysis. Thus, the apparent lack of covalent binding of reverse-BPDE to DNA in cell cultures is not due to an inherent inability to physically interact with DNA. (no Refs)

30. INDIRECT IMMUNOFLUORESCENT LOCALIZATION OF BENZO[A]PYRENE ADDUCTED TO NUCLEIC ACIDS IN CULTURED MOUSE KERATINOCYTE NUCLEI.

Poirier MC, Stanley JR, Beckwith JB, Weinstein IB, Yuspa SH
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Carcinogenesis; 3(3):345-348 1982

The localization of benzo[a]pyrene-deoxyguanosine adducts was studied by indirect immunofluorescence in cultured BALB/c epidermal cells exposed to (+-)7alpha,8alpha-dihydroxy-9alpha,10alpha-epoxy 7,8,9,10-tetrahydrobenzo[a] pyrene (the anti-isomer) utilizing an antiserum specific for the major benzo[a]pyrene-deoxyguanosine adduct in DNA. This antiserum does not cross-react with benzo[a]pyrene or DNA alone. When cultured keratinocytes were incubated with the carcinogen for 1 hr, the immunofluorescence was localized in the nucleus as intense spots on a background of diffuse fluorescence. Fluorescence was absent from cells not exposed to carcinogen and from carcinogen-exposed cells incubated with normal rabbit serum in place of the antiserum. Fluorescence was abolished when the specific antiserum was absorbed with the immunogen DNA prior to incubation with cells, and substantially diminished when exposed cells were preincubated with deoxyribonuclease before the application of the specific antiserum. Incubation of exposed cells with ribonuclease prior to incubation with the specific antiserum removed the bright fluorescent spots and resulted in fluorescent nuclei containing dark spots in similar frequency. Dose-response studies in which benzo[a]pyrene-deoxyguanosine adducts were quantified by enzyme-linked immunosorbent assay and compared with intensity of immunofluorescence demonstrated that decreasing doses of the carcinogen resulted in fewer numbers of adducts as well as proportionally less fluorescence. When cells were exposed to non-toxic doses of the activated carcinogen for 1 hr, nuclear fluorescence was detectable in immediately-fixed cells but faded to non-detectable levels when cells were washed and cultured for an additional 24-48 hr before fixation. (Author abstract) (17 Refs)

31. 7,12-DIMETHYLBENZ[A]ANTHRACENE-DEOXYRIBONUCLEOSIDE ADDUCT FORMATION IN VIVO: EVIDENCE FOR THE FORMATION AND BINDING OF A MONOHYDROXYMETHYL-DMBA METABOLITE TO RAT LIVER DNA.

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Carcinogenesis; 3(3):297-301 1982

The polycyclic aromatic hydrocarbon, 7,12-dimethyl benz[a]anthracene (DMBA) is a potent carcinogen to the female Sprague-Dawley rat, and when administered under conditions that have been shown to produce cancer, results in extensive formation of hydrocarbon-deoxyribonucleoside adducts. Sephadex LH-20 and reverse-phase hplc and spectrofluorometric analysis of these adducts demonstrate that at least one adduct results from the binding of 7,12-dimethylbenz[a]anthracene-1,2,3,4-tetrahydro-3,4 dihydroxy-1,2-oxide. In these experiments, employing ip administration of the hydrocarbon, a second more polar adduct was observed. Evidence is presented that this adduct results from the formation of a monohydroxymethyl-methylbenz[a]anthracene-A-ring-diol epoxide. While both of the monohydroxymethyl-DMBA metabolites have been shown to bind cellular DNA following their administration this is the first evidence of monohydroxymethyl-DMBA-deoxyribonucleoside adducts being formed after the administration of DMBA per se. The evidence suggests that this more polar adduct is a 7-hydroxymethyl-12-methylbenz[a]anthracene deoxyribonucleoside adduct. (Author abstract) (35 Refs)

32. THE FORMATION OF BENZO[A]PYRENE - DEOXYRIBONUCLEOSIDE ADDUCTS IN VIVO AND IN VITRO.

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(c/o Cohen) Toxicology Unit, Dept. Pharmacology, Sch. Pharmacy, Univ. London, 29/39 Brunswick Square, London, WC1N 1AX, England
Carcinogenesis; 3(3):267-273 1982

The formation of DNA-bound products from benzo[a]pyrene was studied using metabolic activation systems of widely differing cellular and structural integrity. The nature of the benzo[a]pyrene-metabolite-deoxyribonucleoside adducts formed was markedly dependent on the nature of the activation system used. Systems where cellular integrity is preserved, namely mouse skin in vivo and rat liver hepatocytes and lung explants in vitro, when treated with benzo[a]pyrene, formed deoxyribonucleoside adducts of which the major one co-chromatographed with a bay-region diol epoxide-deoxyguanosine adduct, 10beta-(deoxyguanosin-N2-yl)-7beta,8alpha,9alpha trihydroxy-7,8,9, 10-tetrahydrobenzo[a]pyrene. In striking contrast, the use of activating systems with disrupted cellular integrity such as rat liver, rat lung and mouse skin microsomal fractions, in the presence of benzo[a]pyrene and exogenous DNA, resulted in the formation of deoxyribonucleoside adducts derived predominantly from either a further metabolite of 9-hydroxybenzo[a]pyrene or (+-)benzo[a]pyrene-4,5-epoxide. The consequences of such results are important when considering the widespread use of subcellular fractions such as microsomes as metabolic activating systems for short-term mutagenicity and carcinogenicity tests. (Author abstract) (41 Refs)

33. RAT MAMMARY GLAND CARCINOGENESIS AFTER LOCAL INJECTION OF N-HYDROXY-N-ACYL-2-AMINOFLUORENES: RELATIONSHIP TO METABOLIC ACTIVATION.

Allaben WT, Weeks CE, Weis CC, Burger GT, King CM
Div. Carcinogenesis, Natl. Center Toxicological Res., HFT-110, Jefferson, AR, 72079
Carcinogenesis; 3(3):233-240 1982

A single local injection of 2.5 umol of N-hydroxy-N-formyl-2-aminofluorene (N-hydroxy-FAF), N-hydroxy-N-acetyl-2-aminofluorene (N-hydroxy-AAF), or N-hydroxy-N-propionyl-2-aminofluorene (N-hydroxy-PAF) to each of the six left mammary glands of female Sprague-Dawley derived CD rats gave a mammary tumor incidence, after 12 mo, of 53% for the N-acetyl 41% for the N-formyl and 33% for the N-propionyl derivatives of N-hydroxyl-N-2 aminofluorene. When N-acetyl-2-aminofluorene (AAF) was applied as above there was only an 8% mammary tumor incidence. Arylhydroxamic acid N,O-acyltransferase activity has been demonstrated in the mammary glands of male, and lactating and non-lactating female Sprague-Dawley derived CD rats by means of a nucleic acid binding assay. Mammary gland cytosol catalyzed tRNA adduct formation to a greater extent with N-hydroxy-FAF. AAF was not activated by this enzyme. Ammonium sulfate fractionation demonstrated the presence of two enzymes, one specific for N-hydroxy-FAF, the other specific for N-hydroxy-AAF and N-hydroxy-PAF. Gel filtration chromatography of mammary gland cytosol demonstrated the presence of two enzymes of differing acyl specificity. Mammary gland microsomes catalyzed the formation of tRNA adducts, but only with the N-hydroxy-FAF derivative. Assays that tested the mutagenic potential of the arylhydroxamic acids in Salmonella typhimurium TA-1538 with either mammary gland cytosol or microsomes demonstrated the order of mutagenicity to be N-hydroxy-FAF much greater than N-hydroxy-AAF greater than N-hydroxy-PAF. A similar order of mutagenicity was demonstrated without an external metabolic activation system. These data demonstrate the presence of two distinct enzymes in the rat mammary gland that activate arylhydroxamic acids. (37 Refs)

EFFECT OF CARCINOGENS ON MACROMOLECULAR SYNTHESES

34. DNA REPLICATION AND CELL-CYCLE PROGRESSION OF CULTURED MOUSE FM3A CELLS AFTER TREATMENT WITH 8-METHOXYPSORALEN PLUS NEAR-UV RADIATION.

Hyodo M, Fujita H, Suzuki K, Yoshino K, Matsuo I, Ohkido M
Dept. Molecular Biology, Tokai Univ. Sch. Medicine, Boseidai, Isehara-shi, Kanagawa-ken, 259-11, Japan
Mutat Res; 94(1):199-211 1982

The effect of 8-methoxypsoralen (MOP) plus near-UV radiation upon cell-cycle progression and macromolecular synthesis was investigated in cultured mouse FM3A cells. An inhibition of cell growth was observed with increasing doses of MOP plus near-UV. The minimum doses that inhibited cell growth were 0.1 ug MOP/ml plus 5 kilojoules (kJ)/square meter (m2) or 1 ug/ml plus 1 kJ/m2. Treatment with MOP (1.0 ug/ml) or near-UV (10 kJ/m2) alone had no effect upon cell growth. When cells were exposed to 1 kJ/m2 and incubated in the presence of 1.0 ug MOP/ml for up to 30 hr, cell distribution through the cell cycle did not change until after 6 hr of treatment. After 12 hr of incubation, the G1 peak became smaller. After 18 hr, more cells were shifted toward the G2 phase, while after 24 hr, most of the cells were at the G2-M peak. This profile did not change even after a prolonged incubation of 30 hr. These results indicated that treated cells were arrested at the G2-M phases. When cells were exposed to 2.5 kJ/m2 in the presence of 1.0 ug MOP/ml, the same tendency for G2-M arrest was observed, but with an increased latency. Immediately after cells were treated with 1.0 ug MOP/ml plus 1 kJ/m2 of near-UV, 3H-thymidine incorporation fell to 40% of control value with subsequent increase after 8 hr to 70%. RNA and protein synthesis were stimulated by low doses of MOP plus near UV, but inhibited by very high doses. (33 Refs)

35. DOSE-RELATED EFFECTS OF PSORALEN AND ULTRAVIOLET LIGHT ON THE CELL CYCLE OF MURINE MELANOMA CELLS.

Varga JM, Wiesehahn G, Bartholomew JC, Hearst JE
Dept. Dermatology, Yale Univ. Sch. Medicine, New Haven, CT, 06510
Cancer Res; 42(6):2223-2226 1982

Cloudman (S91) murine melanoma cells were treated with 4'-hydroxymethyltrioxsalen (HMT), a bifunctional psoralen and exposed to long-wavelength (365 nm) ultraviolet light. DNA content of the cells stained with propidium iodide was measured by flow cytometry, and cell cycle phases were delineated from the DNA histograms by using a curve-fitting routine. We found HMT in combination with long-wavelength (365 nm) ultraviolet irradiation blocked melanoma cells in different phases of the cell cycle, depending on the dose of long-wavelength (365 nm) ultraviolet light and the concentration of HMT. The binding of [3H]HMT to DNA was measured parallel with cell cycle analyses. Treatments with HMT at concentrations corresponding to about 1 HMT bound per 10(6) base pairs of DNA led to the accumulation of cells with predominantly G2 DNA content. At higher concentrations (2 to 3 HMT/10(6) base pairs), the cells were blocked in the S and G1 phases. In conclusion, we have shown that extremely sparse substitution of HMT to DNA blocks melanoma cells in the G2 phase or other phases of the cell cycle in a dose-dependent manner. (Author abstract) (24 Refs)

36. CHLOROACETALDEHYDE, A VINYL CHLORIDE METABOLITE, INDUCES ERRORS DURING IN VITRO DNA SYNTHESIS (MEETING ABSTRACT)

Hall JA, Saffhill R
Christie Hospital and Holt Radium Institute, Manchester, England
Br J Cancer; 44(2):272 1981

Chloroacetaldehyde (CA), a rearranged metabolic product of the human carcinogen vinyl chloride, has been shown to be mutagenic in certain microbial systems as well as towards mammalian cells. CA has been reacted with the alternating DNA-like polymers poly(dA-dT) and poly(dC-dG) when, as with DNA, etheno-adducts of the adenine and cytosine bases are formed. These treated polymers, when used as templates for Escherichia coli DNA polymerase I, show a decreased ability to direct DNA synthesis. This is accompanied by an increase in the relative levels of non-complementary nucleotides incorporated into the newly synthesized DNA-like material. This increased with the amount of modified base present in the templates used. With the poly(dA-dT) templates one dGMP (guanosine monophosphate) residue was incorporated for every 60 +/- ethenoadenine residues present, while no dCMP (cytidine monophosphate) misincorporation was detected. One misincorporation of dAMP or dTMP (thymidine monophosphate)

occurred in the presence of 30 +/- and 80 +/- ethenocytosine residues respectively in the poly(dC-dG) templates. For the modified poly(dC-dG) templates, a nearest-neighbor analysis shows that the majority of the errors were incorporated opposite the cytosine (or modified cytosine) bases. Extensive analyses of the modifications present in the templates indicate that the misincorporations observed are not due to the presence of apurinic sites or to the formation of uracil or xanthine by deamination of the cytosine or adenine bases respectively. We conclude that the non-complementary nucleotide incorporations probably arise from the presence of etheno-adducts in the templates used. (no Refs)

37. ACTION SPECTRA FOR 8-METHOXYPSORALEN AND 3-CARBETHOXYPSORALEN IN SKIN FIBROBLASTS IN VITRO.

Christophers E, Schmidt B

Dept. Dermatology, Univ. Kiel, Schittenhelmstr. 7, D-2300 Kiel, W. Germany

Arch Dermatol Res; 272(3/4):245-250 1982

DNA synthesis was measured in guinea pig skin fibroblasts exposed to 8-methoxypsoralen (8-MOP: 0.01-10 ug/ml) or 3-carbethoxypsoralen (3-CP: 0.1-50 ug/ml) and UV (338.5-423 nanometers, 0.1 Joules/cm(2)). A linear decrease in photoinhibition of DNA synthesis with increasing wavelengths was seen after 8-MOP treatment, whereas 3-CP showed markedly reduced photoinhibition between 350 and 365 nanom. Results demonstrate that the UV action spectra should be considered when using furocoumarin derivatives in clinical practice. (23 Refs)

38. FIBRE AUTORADIOGRAPHY OF REPAIR AND REPLICATION IN DNA FROM SINGLE CELLS: THE EFFECT OF DNA SYNTHESIS INHIBITORS.

Ockey CH

Paterson Lab., Christie Hosp., Holt Radium Inst., Withington, Manchester M20 9BX, England

Eur J Cell Biol; 27(1):25-33 1982

DNA fiber autoradiography, after incorporation of high specific activity 3H-thymidine and 3H-deoxycytidine, has been used to investigate repair in DNA fibers from single cells following UV, or methyl-methane sulfonate (MMS) treatment. Asynchronously growing human fibroblasts, leukocytes, and HeLa cells at different phases of the cell cycle have been investigated. Isotope incorporation in repair could be differentiated from the involved in replication by the distribution and density of silver grains along the DNA fibers. Grain distribution due to repair was continuous over long stretches of the fibers and was at a low density, occasionally interspersed with short slightly denser segments. Replication labeling on the other hand, was dense and usually in short tandem segments. Repair labeling was of a similar overall density in fibers from a single cell, but differed in intensity from cell to cell. In mutagen treated Go (leukocytes) or G1 (HeLa cells), repair labeling was not increased by the presence of the DNA inhibitors, hydroxyurea (HU) or 5-fluorodeoxyuridine (FUdR). Repair was not detectable in S cells however without the use of these inhibitors to reduce endogenous nucleoside production. FUdR enhanced the repair labeling in S cells only slightly, while HU increased it beyond that observed in UV irradiated, HU treated, G1 cells. The intensity of repair labeling in fibers from mutagen treated S cells appears to be proportional to the degree of reduction of DNA chain elongation in replicons. (Author abstract) (23 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

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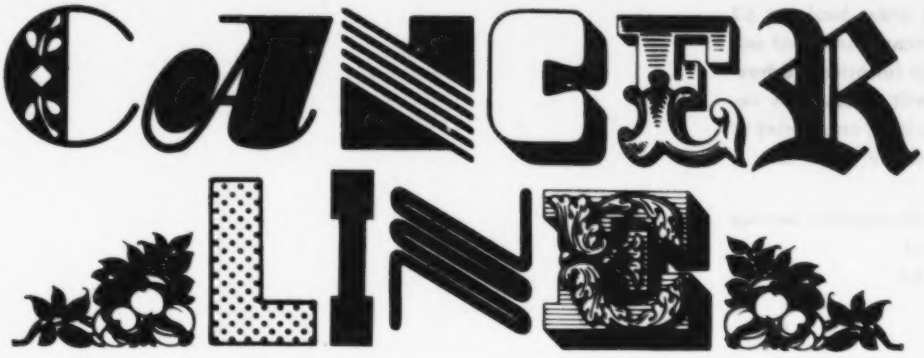

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Macromolecular Alteration and Repair

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BIOLOGICAL ASPECTS OF DNA ALTERATION AND REPAIR IN RELATION TO CARCINOGENICITY

1. INCREASED RATE OF REPAIR OF ULTRAVIOLET-INDUCED DNA STRAND BREAKS IN MITOGEN STIMULATED LYMPHOCYTES.

Hamlet SM, Lavin MF, Jennings PA
Dept. Biochemistry, Veterinary Pathology, and Public Health, Univ. Queensland, Brisbane, 4067, Queensland, Australia
Int J Radiat Biol; 41(5):483-491 1982

Previous results from this laboratory have shown that phytohemagglutinin-stimulated bovine lymphocytes exhibit a peak of ultraviolet-induced DNA repair synthesis 3 to 4 days after addition of mitogen. The level of repair synthesis was approx 10 fold higher than that in unstimulated lymphocytes. We have extended these studies to examine the rate of repair of strand breaks in UV-irradiated bovine lymphocytes. The extent of breakage of DNA was shown to be the same in mitogen-stimulated and unstimulated lymphocytes from two breeds of cattle, when determined by sedimentation of nucleoids on sucrose gradients. However, in mitogen-stimulated cells the time taken

HE 20.3173/2:

to repair DNA strand breaks was 6 hours compared to 12 hours in stationary phase lymphocytes after a UV dose of 5 J/m2. These results suggest that the increased rate of repair of strand breaks is due to the induction of enzymes involved at the post-incision stage of DNA repair. Thus the increased level of repair synthesis observed in earlier work correlates with an increased rate of repair of DNA strand breaks in phytohemagglutinin-stimulated bovine lymphocytes. (Author abstract) (20 Refs)

BIOLOGICAL ASPECTS OF DNA ALTERATION AND REPAIR IN RELATION TO MUTAGENICITY

2. PHOTOACTIVATED AFLATOXINS ARE MUTAGENS TO SALMONELLA TYPHIMURIUM AND BIND COVALENTLY TO DNA IN VITRO.

Israel-Kalinsky H, Tuch J, Roitelman J
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Carcinogenesis; 3(4):423-429 1982

The mutagenesis of Salmonella typhimurium TA100 and covalent binding in vitro of photoactivated aflatoxin B1 (AFB1), aflatoxin B2 (AFB2), aflatoxin G1 (AFG1) and aflatoxin G2 (AFG2) were investigated. Covalent binding levels of 1,140, 225, 330 and 8 pmol aflatoxin per umol nucleotide phosphate were obtained for AFB1, AFG1, AFB2 and AFG2, respectively, at 50 uM mycotoxin after 2hr of irradiation. Mutant frequencies to histidine prototrophy were 97, 19, 49 and 0 x 10(-6) for AFB1, AFG1, AFB2 and AFG2 respectively, after 2 hr irradiation at 100 uM mycotoxin in the surviving fraction of the mutagenized cultures. Toxicity to Salmonella was 0.59, 0.03, 0.31 and 0 lethal hits under the conditions specified for mutagenesis for AFB1, AFG1, AFB2, and AFG2, respectively. (Author abstract) (29 Refs)

3. THE METABOLISM OF NITRO-SUBSTITUTED POLYCYCLIC AROMATIC HYDROCARBONS IN SALMONELLA TYPHIMURIUM (MEETING ABSTRACT)

Andrews P, McCalla DR, McCarry BE, Messier F, Quillain MA
Departments of Chemistry and Biochemistry, McMaster University, Hamilton, Ontario, Canada
Toxic Substances in the Environment, December 12-13, 1981, Kingston, Ontario. Queen's University 11 pp., 1981.

It has been shown by a number of researchers that nitro-substituted polycyclic aromatic hydrocarbons (nitro-PAHs) are direct acting bacterial mutagens. While the environmental hazard posed by these agents is not yet fully clear, these chemicals are known to be formed readily (a) by the nitration of PAHs with NOX in air particulates and diesel exhaust and (b) during the preparation of some types of carbon black. We have been studying the metabolism of 1-nitropyrene in order to gain an understanding of the mechanism of action of these mutagens. The metabolism of 1-nitropyrene by intact cells of Salmonella typhimurium TA98 proved to be slow; much slower than that of nitroheterocyclic compounds like nitrofurans. The principal metabolites proved to be 1-aminopyrene and N-acetyl-1-aminopyrene. Work continues on the characterization of several minor metabolites. When tritiated 1-nitropyrene was incubated with S typhimurium radioactivity became tightly associated with DNA. After the isolated DNA was enzymatically hydrolyzed to its constituent nucleosides, this radioactivity appeared in low molecular weight components. The amount of tritium associated with DNA was time and dose dependent and was markedly reduced in a mutant strain known to have reduced nitroreductase activity. Also, less radioactivity was found in the DNA of a repair-proficient strain than in the DNA of repair-deficient strains. We are currently characterizing the nucleoside-'nitropyrene' adducts by chromatography and mass spectrometry. (no Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN VERTEBRATES

4. ADP-RIBOSYLTRANSFERASE ACTIVITY IN CULTURED HEPATOCYTES. INTERACTIONS WITH DNA REPAIR.

Althaus FR, Lawrence SD, Sattler GL, Pitot HC
McArdle Lab. for Cancer Res., Univ. Wisconsin Medical Sch., Madison, WI, 53706
J Biol Chem; 257(10):5528-5535 1982

A rapid increase in ADP-ribosyltransferase activity was observed when freshly isolated hepatocytes derived from adult rats were established in primary monolayer culture. (ADP-ribose)n-degrading activity remained constant over a period of 48 hr of culture. Inhibition of ADP-ribosyltransferase activity with pyridine derivatives, 3-aminobenzamide, theophylline, or thymidine, was accompanied by an enhanced DNA repair synthesis in response to the direct-acting carcinogen, methyl methanesulfonate, or UV irradiation. Three aminobenzamides differing only in the position of the amino group exhibited the same structure-activity relationship in regard to their action on DNA repair synthesis and ADP-ribosyltransferase. Spermine treatment of hepatocytes apparently had an inverse effect on both these cellular functions. The removal of DNA strand breaks following methyl methanesulfonate treatment was accelerated by inhibitors of ADP-ribosyltransferase. The results suggest that ADP-ribosylation interacts with late stages in the process of DNA repair. This interaction apparently is dependent on the nature of damage imposed on chromatin since repair synthesis in response to a number of carcinogens is unaffected by inhibitors of ADP-ribosyltransferase. (Author abstract) (52 Refs)

5. EUKARYOTIC DNA REPAIR IS BLOCKED AT DIFFERENT STEPS BY INHIBITORS OF DNA TOPOISOMERASES AND OF DNA POLYMERASES ALPHA AND BETA.

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Biochim Biophys Acta; 697(1):6-13 1982

Inhibitors of (a) DNA topoisomerases (novobiocin and nalidixic acid) and of (b) eukaryotic DNA polymerases alpha (cytosine arabinoside) and beta (dideoxythymidine) blocked different steps of DNA repair, demonstrated by the effects of the inhibitors on the relaxation of supercoiled DNA nucleoids following treatment of human cell cultures with ultraviolet light (1-3 J/m2) or N-methyl-N-nitro-N-nitrosoguanine MNNG (5 or 20 uM) and the subsequent restoration of the supercoiled nucleoids during repair incubation. Changes in the supercoiling of nucleoid DNA were assayed by analysis of their sedimentation profiles in 15-30% neutral sucrose gradients. Inhibition of repair by novobiocin was partially reversible; upon its removal

from the culture medium, the nucleoid DNA of repairing cells became relaxed. The DNA polymerse inhibitors allowed the initial relaxation of DNA after treatment of the cells with UV or MNNG but delayed the regeneration of the initial rapidly-sedimenting (supercoiled) nucleoid DNA for 2-4 hr. Dideoxythymidine (1 mM) was more effective than cytosine arabinoside (1 uM) in producing this delay, but neither inhibitor by itself blocked repair permanently. Incubation of ultraviolet-irradiated cells with 1 uM cytosine arabinoside plus 1 mM dideoxythymidine blocked the completion of repair for 24 hr, whereas incubation with 10 uM cytosine arabinoside or 5 mM dideoxythymidine produced only temporary repair delays of 2-4 hr. Thus, it is likely that the two DNA polymerase inhibitors act upon separate targets and that both targets are involved in repair. It is concluded from these and from previous studies that (1) the DNA repair-sensitive target of novobiocin and nalidixic acid in vivo is not a DNA polymerase, but, rather, a DNA topoisomerase; (2) this target affects an initial step of DNA repair leading to the relaxation of supercoiled DNA; (3) the DNA polymerization step of repair may involve both alpha- and beta-type DNA polymerases; and (4) in repair one type of DNA polymerase may substitute for another. (Author abstract) (33 Refs)

6. DISSOCIATED OCCURRENCE OF SINGLE-GENE MUTATION AND ONCOGENIC TRANSFORMATION IN C3H 10T1/2 CELLS EXPOSED TO ULTRAVIOLET LIGHT AND CAFFEINE.

Chan GL, Little JB
Dept. Pathology, Harvard Medical Sch. and Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
J Cell Physiol; 111(3):309-314 1982

Effects of caffeine and UV light on postreplication repair were studied in C3H mouse embryo-derived 10T1/2 cell clones between passages 11-15. Alkaline sucrose gradient sedimentation experiments showed that the DNA synthesized by 10T1/2 cells after UV irradiation was of reduced mol wt when compared to parental DNA. When cells were exposed to 1 milliM caffeine after UV irradiation the DNA repair was severely inhibited. Results indicated that caffeine potentiated the killing of 10T1/2 cells by UV light. Caffeine was effective in enhancing cell killing at all UV doses tested although the differential effects between 0.5 and 1 milliM were less pronounced at higher UV doses. With UV doses of 5 and 10 Joule/square meter (J/m2), the addition of caffeine resulted in higher transformation frequencies. The rate of increase at two UV doses were 2.4- and 2.3-fold/milliM caffeine, respectively. When the transformation of unirradiated cells exposed to caffeine for 48 hr was measured, caffeine alone induced transformation. However, the transformation potentiation effect of 1 milliM caffeine after 10 J/m2 was statistically significant. The potentiation factor was 1.7. Caffeine by itself did not induce detectable ouabain-resistant mutations in 10T1/2 cells; a possible inhibitory effect was observed. Results indicate that gene mutation and malignant transformation in 10T1/2 cells can be dissociated. (45 Refs)

7. MEASUREMENTS BY FILTER ELUTION OF DNA SINGLE- AND DOUBLE-STRAND BREAKS IN RAT HEPATOCYTES: EFFECTS OF NITROSAMINES AND GAMMA-IRRADIATION.

Bradley MO, Dysart G, Fitzsimmons K, Harbach P, Lewin J, Wolf G
Merck Inst. Therapeutic Res., West Point, PA, 19486
Cancer Res; 42(7):2592-2597 1982

This work presents a filter elution method for measuring DNA single- and double-strand breaks in primary rat hepatocytes without radioactive labeling of DNA. We have studied the effects of a series of nitrosamines and of gamma-irradiation on DNA single- and double-strand break induction. The repair of DNA single-strand breaks in the hepatocytes was measured after treatment with 60Co, 1-methyl-1-nitrosourea, and N-nitrosodimethylamine. The hepatocytes were isolated by ethylene glycol-bis(beta-aminoethyl ether)-N,N'-tetra acetic acid-collagenase perfusion and had a mean viability of 91 +-4% (SD). The isolated cells were treated for varying lengths of time with nitrosamines in suspension culture in L-15 medium containing 10% fetal bovine serum. After treatment, the cells were chilled, loaded onto 2-um polycarbonate filters, and lysed in a 2% sodium dodecyl sulfate-proteinase K solution, pH 9.6. The DNA was eluted from the filter at either native or denaturing pH with fractions collected every 3 hr. The quantity of DNA in each fraction was determined by measuring the fluorescent product formed between it and diaminobenzoic acid after ethanol-sodium acetate precipitation and trapping of the DNA on 0.2-um polycarbonate filters. The results show that the carcinogens, N-nitrosodimethylamine, N-nitrosodiethylamine, N-nitrosodipropylamine, N-nitrosodibutylamine, and 1-nitrosopiperidine all made dose- and time-related increases in the number of single-strand breaks in rat hepatocytes. N-Nitrosodiphenylamine produced small numbers of single-strand breaks. No double-strand breaks were formed by any of the nitrosamines. Single-strand breaks induced by N-nitrosodimethylamine were repaired very slowly relative to repair of either gamma-ray or 1-methyl-1-nitrosourea-induced single-strand breaks. This system has many advantages for studying carcinogen metabolism and DNA damage in hepatocytes, one of the major target cells for many carcinogens. (Author abstract) (19 Refs)

8. KINETICS OF REPAIR OF DNA SINGLE-STRAND BREAKS IN CULTURED MAMMALIAN CELLS. PART I. THE DEPENDENCE ON IRRADIATION DOSE AND CELL CYCLE STAGE.

Vexler FB, Kublik LN, Eidus LK, Vexler AM
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Int J Radiat Biol; 41(4):453-457 1982

Kinetics of repair of DNA single-strand breaks were examined in asynchronous cultures of Chinese hamster cells and in cells synchronized at the G1 stage after irradiation with doses of 15 and 200 grays (Gy), which induce reproductive and interphase death of cells, respectively. Irradiation led to practically the same DNA degradation independent of cell cycle stage. In all experiments with asynchronous cultures, repair started immediately after irradiation with 15 and 200 Gy and did not depend on the pH of the medium in the range 6.5-8.0. The major part of the strand breaks repaired quickly enough. Following exposure to 15 Gy, the repair proceeded at a constant rate in both cultures; however, the repair rate was twice as low in synchronous as in asynchronous cultures. After irradiation with 200 Gy, the repair processes in both cultures started with the rates close to those at a lower dose. However, 5 min later, the repair rates became about 5-6x lower in asynchronous cultures; in asynchronous cultures, it was 2x as low as that in asynchronous cultures. Then the rates remained practically constant in both cultures. (14 Refs)

9. INTERCELLULAR CO-OPERATION IN REPAIRING RADIATION-INDUCED SINGLE-STRAND DNA BREAKS.

Edgren M
Dept. Tumor Biology II, Karolinska Inst. Medical Sch., 104 01 Stockholm, Sweden
Int J Radiat Biol; 41(5):589-593 1982

The role of glutathione (GSH) in the contact effect, the enhanced rejoining of single-strand DNA breaks (ssb) in cells irradiated while in close contact, was examined using an experimental system with GT-deficient (GSH-) and GSH-proficient (GSH+) human sc fibroblasts. Rejoining of ssb in GSH- cells proceeded at a decreased rate; not more than approx 70% of the radiation-induced breaks were repaired within 1 hr when incubated either in buffer solution or in complete medium. Post-irradiation treatment of GSH- cells with GSH increased the rejoining capacity of GSH- cells to normal levels when added immediately after irradiation. Admixture of GSH+ cells to irradiated GSH- cells in a proportion 2:1 also enhanced ssb rejoining capacity. Heavily irradiated GSH+ cells appeared to have a slightly greater effect in enhancing ssb repair than unirradiated cells. Mixing irradiated and unirradiated GSH- cells in a proportion of 1:2 does not appreciably influence the rate of ssb rejoining. When the number of unirradiated GSH- cells in the cell mixture was 15x larger than the number of irradiated GSH- cells, ssb rejoining was enhanced, but remained below the normal level after 1 hr of incubation. Medium conditioned with GSH+ cells slightly enhanced rejoining, while conditioning with GSH- cells was slightly inhibitory. The results indicated that some part of the cellular rejoining process of ssb requires the presence of GSH or some other specific aminothiol. (19 Refs)

10. CRITICAL PERIODS DURING THE IN SITU REPAIR OF RADIATION-INDUCED DNA DAMAGE IN RAT CEREBELLAR NEURONS AND 9L BRAIN TUMOR CELLS.

Wierowski JV, Thomas RR, Ritter P, Wheeler KT
Div. Radiation Oncology, Univ. Rochester Cancer Center, Box 704, 601 Elmwood Ave., Rochester, NY, 14642
Radiat Res; 90(3):479-488 1982

The existence of critical periods during repair of radiation-induced DNA damage such that a second dose delivered during these periods causes an accumulation of DNA damage was investigated. DNA repair kinetics for cerebellar neurons and intracerebral 9L tumor cells from the same rat were assayed following the second of two 1,250 rad doses of 137Cs gamma rays separated by various intervals. At the time of the second 1,250 rad exposure, the amount of DNA damage remaining from the first 1,250 rad exposure was 44 rad equivalents or less in tumor cells, and 184 rad equivalents or less in neurons. Alterations in the neuronal DNA repair kinetics observed in the 15 min split-dose experiment were found to be specifically related to the events that occurred or were occurring at the time the second dose was delivered. In neuronal DNA profiles exhibiting an increased amount of DNA sedimenting greater than 250 S in the 15-min split dose experiments, the amount of DNA sedimenting greater than 300 S was also found to be significantly greater than that from unirradiated controls. The physiological consequences of the apparent accumulation of DNA damage observed in split-dose experiments are unknown. For intervals greater than or equal to 15 min between the two 1,250 rad exposures, no critical periods were found in intracerebral 9L tumor cells. An interval of 15 min to 1 hr between doses appeared to be a critical period for cerebellar neurons, resulting in an increase in fast sedimenting DNA. Molecular events leading to this increase in fast-sedimenting DNA after the second dose remain unknown. Application of this work to clinical radiotherapy is discussed. (15 Refs)

11. REPAIR OF DOUBLE STRAND BREAKS IN X-IRRADIATED EHRLICH ASCITES TUMOUR CELLS AND THE EFFECTS OF THE DNA INHIBITOR BETA-ARA A (MEETING ABSTRACT)

Bryant PE, Blocher D
GSF-Abteilung fur Biophysikaliache Strahlenforschung, 20 Paul Ehrlich Strasse, 6000 Frankfurt/M, W. Germany
Molecular and Cellular Mechanisms of Irradiation, March 17-19, 1982, Neuherburg, W. Germany. Gesellschaft fur Strahlen und Umweltforschung MBH 65 pp., 1982.

The repair of DNA dsb has been followed in cells after x-irradiation using the unwinding and the neutral sucrose centrifugation methods. Dsb, induced with a frequency of 40 dsb/cell/Gy, repaired with a time constant t37 equals 2-4h. Beta-ara A strongly inhibited dsb repair; the inhibition was complete at about C equals 400 umol/l. Experiments designed to simulate the procedure used in plating of cells to measure survival, showed that when Beta-ara A was washed away from cells after treatment, the repair of dsb returned. Beta-ara A has been shown to remove the shoulder from the survival curve of this cell line (Iliakis 1980), therefore it was of interest to measure the breaks remaining at longer times following irradiation. Although repair of dsb returned after washing away the drug, it was found that more breaks persisted in Beta-ara A treated cells than in the control untreated cells. A larger number of dsb were also measured at times corresponding to the time of first cell division, in lightly irradiated cells. These additional dsb may contribute to the increased yield of chromosome aberrations observed, after irradiation and Beta-ara A treatment, at first mitosis which probably cause the increased cell killing observed. It is postulated however that an increased level of misjoining of DNA strands also contributes to the increased aberration formation seen after Beta-ara A treatment of irradiated cells. (2 Refs)

12. DAMAGE TO RAT LIVER DNA FROM IN VIVO EXPOSURE TO MONOCROTALINE, A PYRROLIZIDINE ALKALOID (MEETING ABSTRACT)

Petry TW, Bowden GT, Huxtable RJ, Sipes IG
Department of Pharmacology and Radiation Oncology, University of Arizona College of Medicine, Tucson, AZ, 85724
Toxicologist; 2(1):102 1982

Pyrrolizidine alkaloids (PAs) are known to damage DNA in vitro, to be hepatocarcinogens in animal models, and have been linked to an increased incidence of hepatic carcinoma among South African Bantus. We have employed alkaline elution to detect and characterize DNA damage resulting from in vivo exposure of male Sprague-Dawley rats (150-280g) to single intraperitoneal doses of the PA, monocrotaline. Hepatic nuclei were isolated, and served as the source of DNA in all experiments. No evidence of single-strand breaks, as would be indicated by an increased rate of DNA elution from the filter as compared to controls, was detected at either 4 or 8 hr after doses of up to 120mg/kg of monocrotaline. As monocrotaline may be bioactivated to bifunctional alkylating agents, experiments were conducted to detect DNA cross-links. In contrast to the results of the single-strand break experiments, evidence for DNA cross-links was observed at doses as low as 5mg/kg, 4 hr after administration of the PA. DNA cross-linking was detected by an apparent decrease in the number of x-ray induced single strand breaks, and consequently a decreased rate of

DNA elution from the filter as compared to controls, when nuclei from both groups were x-irradiated. (no Refs)

13. QUANTITATIVE ASSESSMENT OF CARCINOGEN-MODIFIED DNA IN SPECIFIC LIVER CELL POPULATIONS FOLLOWING A SINGLE DOSE N-2-ACETYLAMINOFLUORENE (AAF) OR ITS N-HYDROXY DERIVATIVE (N-OH-AAF) (MEETING ABSTRACT)

Baranyi BL, Swenberg JA, Goodman JI
Department of Pharmacology and Toxicology, Michigan State University, East Lansing, MI, 48824
Toxicologist; 2(1):103 1982

AAF-induced hepatocarcinogenesis appears to be targeted to parenchymal cells (PC). Our objective was to determine whether or not there is preferential binding of carcinogen (C) residues to the DNA of these target cells and, if so, the possible basis for the selectivity. AAF and its N-hydroxy derivative (N-hydroxyl-N-2-acetylaminofluorene), the first product in the metabolic activation of AAF, were employed for these studies. Male Sprague-Dawley rats weighing 200-250 g were injected, ip, with (ring-3H)AAF or (ring3H)-N-OH-AAF. Animals were sacrificed at either the time of peak binding of C to DNA, 2 hr or 18 post-injection, when N-OH-AAF or AAF, respectively, were used, and at 3 days after maximum binding. PC and non-parenchymal (NPC) cells were isolated by centrifugal elutriation. Following AAF administration, the u moles of adducts formed/mg DNA of PC was 2.7 times that of the NPC. When N-OH-AAF was employed, equal amounts of adducts were found associated with DNA of PC and NPC. By 3 days after the period of maximum DNA binding 50-59% of the adducts initially present remained in the DNA of both cell types following administration of either AAF or N-OH-AAF. These results suggest that AAF preferentially damages DNA of PC due to an increased capacity of these cells to carry out the N-hydroxylation of AAF. (no Refs)

14. MOLECULAR AND CELLULAR MECHANISMS IN CARCINOGENESIS (MEETING ABSTRACT)

Rajewsky MF
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Molecular and Cellular Mechanisms of Irradiation, March 17-19, 1982, Neuherburg, W. Germany. Gesellschaft fur Strahlen und Umweltforschung MBH 65 pp., 1982.

Structural modifications of DNA in cellular chromatin are primary events in the multistage process of tumorigenesis initiated by chemical carcinogens, ionizing radiation, and UV light. Among the various classes of chemical carcinogens, the alkylating agents have been particularly well characterized with regard to their reaction products in DNA, and sophisticated methodology (including the use of monoclonal antibodies) has been developed for the detection of specific alkylation products. It is not yet clear which molecular processes are preferentialiy affected, or set into motion, by carcinogen-modified DNA structures, and which alterations of cellular genetic programmes result in the expression of malignant phenotypes. Among the mechanisms to be considered are different types of mutations, altered patterns of DNN methylation or m-RNA processing, gene rearrangements and amplification, and possibly error-prone DNA repair. There is evidence indicating that in order to become malignantly transformed, cells must be proliferating (or have retained the capacity to re-enter the cell cycle; 'Go-cells') at the time of carcinogen exposure. Furthermore, a number of model systems of carcinogenesis indicate a cell type and differentiation stage-dependency of carcinogenic effect. Certain carcinogen-DNA adducts can be specifically recognized, removed and repaired by cellular enzymes which are expressed to varying degrees in different cell types and tissues, individuals, and species. The differential capacity of cells to repair carcinogen-modified DNA (besides intercellular variations in the metabolic conversion of chemicals to their ultimate reactive derivatives), may constitute one of the determinants for the probability of malignant transformation. (no Refs)

15. THE INDUCTION OF SCE AND CHROMOSOMAL ABERRATIONS WITH RELATION TO SPECIFIC BASE METHYLATION OF DNA IN CHINESE HAMSTER CELLS BY N-METHYL-N-NITROSOUREA AND DIMETHYL SULPHATE.

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Carcinogenesis; 3(4):385-390 1982

Chinese hamster cells (V79) were treated, either as exponentially proliferating cultures or under conditions where they were density-inhibited, with various doses of the potent carcinogen N-methyl-N-nitrosourea (MNU) or the relatively weak carcinogen dimethylsulfate (DMS). The colony forming ability of these cells and the induced frequencies of sister chromatid exchanges (SCEs) and chromosomal aberrations were assayed. Following the exposure of density-inhibited cells to radio-labeled methylating agents (labeled in the methyl group) these phenomena were related to the levels of 7-methylguanine (7-meGua), O6-methylguanine (O6-meGua) and 3-methyladenine (3-meAde) in the DNA. At equitoxic doses MNU and DMS induced similar frequencies of SCEs and chromosomal aberrations. Since, at equitoxic doses, MNU produces approx 20x more O6-meGua in V79 cell DNA than does DMS, this indicates that the formation of O6-meGua in DNA is not a major cause of SCEs and chromosomal aberrations. DMS-induced SCEs may be mediated via the production of both 3-meAde and 7-meGua in the DNA; these two methylated purines may also be responsible for MNU-induced SCEs. Therefore, no one specific methylated purine was identified as being solely accountable for the formation of SCEs. Also, the repair of lesions in the DNA of non-replication V79 cells leads to a reduction in the SCE frequency on their subsequent release from the density-inhibited state, suggesting that repair is not intimately responsible for their formation. No association was discernable between chromosomal aberrations and any of the three methylated purines studied. (Author abstract) (34 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN BACTERIA

16. ROLE OF DNA REPAIR IN ETHYL METHANESULFONATE-INDUCED MUTAGENESIS IN SACCHAROMYCES CEREVISIAE.

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Dept.Radiation Biology and Biophysics, Univ. Rochester Sch. Medicine, Rochester, NY, 14642
Carcinogenesis; 3(4):439-444 1982

Ethyl methanesulfonate (EMS)-induced reversion of two sites which revert preferentially by GC to AT transitions, cycl-131 and cycl-115, has been examined in radiation sensitive, rad,

mutants of yeast belonging to the rad52 epistasis group. The rad50, rad51, rad52, rad54 and rad56 mutants showed reduced reversion of both tester sites when stationary phase diploid cells were treated with EMS. No correlation was found between EMS-induced reversion and EMS-induced homologous mitotic intragenic recombination. Survival of rad6 rad52 double mutants following EMS treatment indicates that there is one epistasis group for the repair of EMS-induced lethal damage in yeast. A model involving misrepair mutagenesis of specific lesions is proposed to account for the experimental results. (Author abstract) (39 Refs)

17. THE ROLE OF INDUCIBLE DNA REPAIR IN W-REACTIVATION AND RELATED PHENOMENA.

Knudson GB
Army Medical Res. Inst. of Infectious Diseases, Frederick, MD
The Role of Inducible DNA Repair in W-Reactivation and Related Phenomena. Available from National Technical Information Service, Springfield, VA, as AD-A108 048/0:, 40 pp., 1981.

Most of the UV-induced photoproducts in the DNA of bacteria and their viruses are repaired by 'error-proof' repair mechanisms such as photoreactivation, ('short-patch') excision repair, and recombinational repair. Single-strand gaps resulting from replication of DNA, which contains pyrimidine dimers, can be repaired by ultraviolet (UV)-inducible, recA + lex+-dependent 'error-prone' repair ('SOS' repair) which leads to mutations in the bacteria and its phages. Other UV-induced recA+ lex+-dependent functions, such as prophage induction, filamentous growth, and W-reactivation, are coordinately regulated with the error-prone repair functions. An increasing amount of experimental evidence suggests that misincorporation of bases could result from an inducible factor which affects the proofreading activities of DNA polymerase, allowing it to fill postreplicative daughter strand gaps across from noncoding UV photoproducts. Mutagenic W-reactivation illustrates the role of UV-inducible, recA+ lex+-dependent functions in the error-prone DNA repair of bacteria and their viruses. (Author abstract)

MACROMOLECULAR BINDING OF CARCINOGENS

18. EFFECT OF HISTONE ACETYLATION ON THE FORMATION AND REMOVAL OF B(A)P CHROMATIN ADDUCTS.

Kootstra A
Dept. Carcinogenesis, Swiss Inst. Experience Cancer Res., CH-1066 Epalinges s/Lausanne, Switzerland
Nucleic Acids Res; 10(9):2775-2789 1982

The modification of core histone proteins in mouse 10T1/2 cells and human lung epithelioid (A549) cells by B(a)PDE ((+-)7a,8beta-dihydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene) in vivo and in vitro was found to be similar. Only histone H2A and H3 were extensively modified. Also other proteins, possibly A24 protein and the minor histone H1 species seem to be binding relatively high levels of this ultimate carcinogen. Butyrate treatment which causes hyperacetylation of the core histones, did not change the specificity of B(a)PDE binding to core histones, nor did it affect the initial level of DNA modification. The acetylated species of histone H3 were all accessible to B(a)PDE, suggesting that these epsilon-amino-groups of the lysine residues are not the targets of the B(a)PDE. The rate of removal of B(a)P-DNA adducts was not affected by butyrate treatment in either normal human or XP fibroblasts. Furthermore, the B(a)P-core histones were not preferentially removed from normal human fibroblast chromatin during a 24 hr post-treatment incubation. (Author abstract) (50 Refs)

19. METABOLISM OF BENZO(A)PYRENE BY HUMAN EPITHELIAL AND FIBROBLASTIC CELLS: METABOLITE PATTERNS AND DNA ADDUCT FORMATION.

Bartley J, Bartholomew JC, Stampfer MR
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J Cell Biochem; 18(2):135-148 1982

The metabolism of benzo(a)pyrene (BaP) and DNA adduct formation were compared in the same incubations of mammary epithelial cells grown out in early passage, from each of three human subjects, and of fibroblasts from one of these subjects. Mammary epithelial cells showed the preferential formation of 7,8-dihydrodiol-9,10-dihydroepoxybenzo(a)pyrene, (BPDE) the ultimate carcinogen. The end products of BaP metabolism in fibroblasts, unlike epithelial cells, were mainly mono- and dihydroxide derivatives of BaP. The greater ease of DNA adduct formation in epithelial cells is apparently related to the metabolites produced from BaP by these cells. The metabolite results indicate that mammary epithelial cells preferably converted BaP to diols, some of which were conjugated with glutathione at the first epoxidation step. The remaining dihydrodiols were readily converted to BPDE, a large portion of which ended up as tetrols and glutathione conjugates, but in the process BPDE was available to react with DNA. The accumulation of diols in the later stages of fibroblast incubations indicates that these cells have a much lower capacity to convert diols to the diolepoxide than do mammary epithelial cells. These results support the theory that chemical carcinogens may be involved in the induction of human breast cancer. (46 Refs)

20. INTERACTION OF BENZO(A)PYRENE AND ITS DIHYDRODIOL-EPOXIDE DERIVATIVE WITH NUCLEAR AD MITOCHONDRIAL DNA IN C3H10T1/2 CELL CULTURES.

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Div. Environmental Sciences, Cancer Center/Inst. Cancer Res., Columbia Univ., New York, NY, 10032
Cancer Res; 42(7):2764-2769 1982

To analyze the distribution of radioactive carcinogens and [3H]thymidine between nuclear DNA (nDNA) and mitochondrial DNA (mtDNA), we have developed a simple and rapid method for the separation of nDNA and mtDNA using gel electrophoresis of cell lysates. Using this method, we found that, when C3H10T1/2 cells are exposed to either 0.5 uM [3H]-(+-)-7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy 7,8,9,10-tetrahydrobenzo(a)pyrene ([3H]BPDE) or 1 uM [3H]benzo(a)pyrene, the mtDNA contains a major fraction of the total adducts formed with cellular DNAs. Deoxynucleoside adducts formed between benzo(a)pyrene and mtDNA in intact C3H10T1/2 cells or between BPDE and isolated rat liver mtDNA were analyzed by high-performance liquid chromatography, and were found to be much more heterogeneous than those present in nDNA of C3H10T1/2 cells. The extensive modification of mtDNA with BPDE in C3H10T1/2 cells is associated with preferential inhibition of the incorporation of [3H]thymidine into ntDNA when compared to incorporation of [3H]thymidine into nDNA. To analyze the factors responsi-

ble for the extensive modification of mtDNA by BPDE, we investigated the role of a lipid phase utilizing liposome:DNA complexes as a model system. We found that the liposomes protect BPDE from spontaneous hydrolysis and enhance the extent of DNA modification at low DNA concentrations. These findings extend previous evidence suggesting that the mitochondria may be important cellular targets in the process of chemical carcinogenesis. (Author abstract) (29 Refs)

21. MODULATION OF EPOXIDE HYDROLASE ACTIVITY. EFFECT ON THE ACTIVATION OF BENZO[A]PYRENE AND ITS COVALENT BINDING TO DNA IN THE NUCLEUS.

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Dept. Pharmacology, Univ. Mainz, D-6500 Mainz, W. Germany
Adv Exp Med Biol; 136(partA):705-716 1982

Role of epoxide hydrolase (EH) in binding 7,8-dihydrodiol-9,10-oxide (DDO) and 9-hydroxy-benzo(a)pyrene-4,5-oxide (HBPO) to DNA was investigated using isolated rat liver nuclei. EH levels were moderated using trans-stilbene oxide (TSO) and trichlorpropilene oxide (TCPO). Male Sprague-Dawley rats were treated with 3-methylcholanthrene (MC) and/or TSO. Patterns of modified nucleosides obtained from incubation of nuclei with 3H-benzo(a)pyrene (BP) are presented. When purified EH in 10-fold excess of the amount present in the nuclei was added to the incubation medium the degree of HBPO binding was diminished in the controls. Similar results were obtained when nuclei from MC plus TSO-treated rats were used. Results of experiments using nuclei and 7.5 mg of microsomal protein from MC-treated rats were very similar to those obtained using nuclei alone, except that the total binding of both BP metabolites was higher. The amount of HBPO binding was lower when the EH activity was increased, but binding of DDO was not changed. When EH was inhibited by TCPO, DDO binding decreased and HBPO increased. Individual pathways of BP metabolism are presented. Results showed that the levels of EH activity greatly influence the amounts and patterns of BP-derived metabolites binding to DNA, and imply that EH activity is an important factor in influencing the in vivo carcinogenicity of BP and other polycyclic hydrocarbons. (35 Refs)

22. SIMILARITIES IN THE FORMATION AND REMOVAL OF COVALENT DNA ADDUCTS IN BENZO(A)PYRENE-TREATED BALB/3T3 VARIANT CELLS WITH DIFFERENT INDUCED TRANSFORMATION FREQUENCIES.

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Cell Genetics Section, Lab. Molecular Carcinogenesis, NCI, Bethesda, MD, 20205
Cancer Res; 42(7):2644-2650 1982

Classes of cell variants isolated from BALB/3T3-A31 clone 1 showing high, intermediate, and low susceptibility to ultraviolet light-induced transformation also demonstrated a differential response to benzo(a)pyrene (BP)-induced transformation. On the other hand, these variants showed an identical susceptibility to the killing effect of these carcinogens. The extent of BP binding to DNA was found to be very similar in all three classes of variants under transforming conditions. BP:DNA adducts from the variant cells were analyzed by high-pressure liquid chromatography. The same adducts (N2- *10S-[7R,8S,9R-trihydroxy-7,8,9-10 tetrahydrobenzo(a)pyrene]yl* deoxyguanosine and a minute amount of the 7S enantiomer) were detected in the highly susceptible, the intermediately susceptible, and the resistant variant clones. Removal of the BP:DNA adduct occurred at an equally slow rate in all three classes of variant cells. These results indicate that the formation of stable covalent DNA adducts is not a sufficient condition for induction of transformation. Processes other than formation and removal of the stably bound BP:DNA covalent adducts are thus major factors controlling the susceptibility of BALB/3T3-A31 clone 1 variant cells to BP-induced transformation. (Author abstract) (46 Refs)

23. COVALENT BINDING OF BENZIDINE AND N-ACETYLBENZIDINE TO DNA AT THE C-8 ATOM OF DEOXYGUANOSINE IN VIVO AND IN VITRO.

Martin CN, Beland FA, Roth RW, Kadlubar FF
Cancer Res. Unit, Univ. York, York YO1 5DD, England
Cancer Res; 42(7):2678-2686 1982

Benzidine, a human urinary bladder carcinogen, induces hepatic tumors in mice and rats. In this study [3H]benzidine was administered in drinking water to mice for 1 wk, and the covalent binding of the carcinogen to hepatic DNA was then determined. A single carcinogen: DNA adduct was detected which decreased in concentration by approx 50% at 1 day after treatment and then remained at a nearly constant level for at least 7 days. Injection of radiolabeled benzidine or N-acetylbenzidine into rats also resulted in a single carcinogen:DNA adduct that was chromatographically identical to that obtained in mouse liver. While administration of benzidine and N-acetylbenzidine resulted in high levels of the adduct in rat hepatic DNA, injection of N,N'-[ring-14C]diacetylbenzidine did not give detectable binding. The same carcinogen:DNA adduct found in rat and mouse liver was prepared synthetically by: (a) hydrolysis of calf thymus DNA reacted with N-hydroxy-N'-acetylbenzidine at pH 5; and (b) reaction of N-acetoxy-N,N'-diacetylbenzidine with deoxyguanosine and subsequent selective deacetylation of the product with methanolic ammonia. Mass and nuclear magnetic resonance spectral data of the synthetic products established the structure of the hepatic adduct as N-(deoxyguanosin-8-yl)-N'-acetylbenzidine. The nonacetylated derivative, N-(deoxyguanosin-8-yl)benzidine, was synthesized by carboxylesterase treatment of N-(deoxyguanosin-8-yl)-N'-acetylbenzidine and was shown not to occur in rat and mouse liver DNA. These data indicate that the metabolic activation of benzidine to an ultimate carcinogen in rats and mice does not involve N-hydroxybenzidine or sulfotransferase-catalyzed activation of N-hydroxy-N,N'-diacetylbenzidine. The remaining pathways for metabolic conversion of benzidine to an ultimate carcinogenic species are discussed in relation to liver and urinary bladder carcinogenesis. (46 Refs)

24. INTERACTION OF REACTIVE INTERMEDIATES WITH DNA.

Magee PN, Chu CK, Gombar CT, Jensen DE, Parchman LG
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Adv Exp Med Biol; 136(partB):1335-1347 1982

Covalent binding of some selected chemicals to rat liver DNA is described and the results related to the proposal by Lutz that the extent of binding may be a quantitative indicator in the process of chemical carcinogenesis. Lutz suggested that covalent binding may be expressed in quantitative terms as the Covalent Binding Index relating damage to DNA as a function of dose. N-nitrosodimethylamine was used as a positive control. No in vivo interaction of N-nitrosoproline with rat liver DNA was observed. Since this compound was rapidly eliminated from the body and a very small degree of metabolism occurred, the use of proline as a safe test compound in studies

on endogenous nitrosation is supported in animals and humans. A very small, but real interaction between trichloroethylene and mouse liver DNA in vivo was observed, supporting the apparent low carcinogenic potency of the compound and doubts concerning its carcinogenicity. In the presence of sulfhydryl compounds, N-nitrosocimetidine interacted with calf thymus DNA in vitro, yielding a pattern of methylated purine bases identical to that produced by N-methyl-N'-nitro-N-nitrosoguanidine (MNG) and other carcinogenic and mutagenic N-nitroso compounds. Preliminary in vivo experiments indicated that the extent of methylation of DNA was much less in organs of animals treated with nitrosocimetidine than those treated with MNG. (37 Refs)

25. METABOLISM AND NUCLEIC ACID BINDING OF 7-FLUORO-2-ACETAMIDOFLUORENE IN RATS: OXIDATIVE DEFLUORINATION AND APPARENT DISSOCIATION FROM HEPATOCARCINOGENESIS OF 8-(N-ARYLAMIDE)GUANINE ADDUCTS ON DNA.

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Chem Biol Interact; 40(1):27-43 1982

The significance in hepatocarcinogenesis of various arylamine/amide adducts with nucleic acid was investigated. Female Fischer and Sprague-Dawley rats are comparably sensitive to hepatocarcinogenesis by 2-acetamidofluorene (AAF), while male rats are more sensitive. 7-Fluoro-2-acetamidofluorene is more carcinogenic in Sprague-Dawley rats than is AAF, and strikingly so toward the liver of female rats. Binding of both compounds to liver nucleic acids was determined for Fischer rats at 1 and 3 days after a single injection of carcinogen, and in female Sprague-Dawley rats from 1 to 28 days after a single injection. No 8-(N-2-fluorenylacetamido)guanine adduct or the 7-fluoro derivative could be found in RNA or DNA of female Sprague-Dawley rats treated with AAF These adducts were present in comparable amounts in both male and female Fischer rats. The binding of 7-fluoro-AAF derivatives was higher than that of AAF derivatives in female Sprague-Dawley rats. Feeding of either AAF or 7-fluoro-AAF to Sprague-Dawley rats for 4 wk before a single injection of [3H]7-fluoro-AAF resulted in reduction of the 8-(N-2-(7-fluoro)fluorenyl-acetamido)guanine adduct in males to undetectable levels in DNA and to 10% of control level in RNA. Non-acetylated adducts were increased in males, but decreased in females by AAF prefeeding; 7-fluoro-AAF prefeeding resulted in little change in adduct formation in females and in a major increase in non-acetylated adducts in males. AAF adducts disappeared from DNA more rapidly than did 7-fluoro-AAF adducts. Assay of the urinary metabolites from the animals in the prefeeding experiment showed that all compounds fed increased the proportion of N-hydroxy-7-fluoro-AAF among the metabolites. Defluorination of 7-fluoro-AAF to 7-hydroxy-AAF was also demonstrated and the ratio of 7-hydroxy-AAF to 5-hydroxy-7-fluoro-AAF was comparable to that observed for 7-hydroxy-AAF/5-hydroxy-AAF and AAF itself, suggesting that fluoro substitution does not increase activity by preventing detoxication. (28 Refs)

26. CYTOCHROME P-450-AND FLAVIN-CONTAINING MONOOXYGENASE-CATALYZED FORMATION OF THE CARCINOGEN N-HYDROXY-2-AMINOFLUORENE AND ITS COVALENT BINDING TO NUCLEAR DNA.

Frederick CB, Mays JB, Ziegler DM, Guengerich FP, Kadlubar FF (c/o Kadlubar) Natl. Center for Toxicological Res., Food and Drug Admin., Environmental Protection Agency, Jefferson, AR, 72079

Cancer Res; 42(7):2671-2677 1982

The metabolic N-oxidation of the carcinogen 2-aminofluorene was examined in vitro using fortified hepatic microsomes from a variety of species. Rat, dog, human, and pig liver microsomes catalyzed the formation of N-hydroxy-2-aminofluorene (N-OH-AF) from AF at rates of 1.6, 1.0, 1.2, and 3.5 nmol/min/mg protein, respectively. The involvement of both cytochrome P-450 and the flavin-containing monooxygenase was demonstrated with hepatic microsomes and with purified enzymes by using specific enzyme inhibitors. 2-[(2,4-Dichloro-6-phenyl)phenoxy]ethylamine, a potent cytochrome P-450 inhibitor, decreased microsomal N-OH-AF formation by 96, 83, 70, and 46% in the rat, dog, human, and pig, respectively; and further addition of methimazole, a high-affinity flavin-containing monooxygenase substrate, abolished the residual N-hydroxylating activity. Using the purified porcine flavin-containing monooxygenase, metabolic formation of N-OH-AF occurred at a rate of 4.9 nmol/min/nmol flavin adenine dinucleotide and was insensitive to 2-[(2,4-dichloro-6-phenyl)phenoxy]ethylamine inhibition. In addition, purified rat liver cytochrome P-450 (isolated from 5,6-naphthoflavone-induced animals) N-hydroxylated AF (1.1 nmol/min/nmol P-450) and was completely inhibited by 2-[(2,4-dichloro-6-phenyl)-phenoxy]ethylamine, but the reaction was insensitive to methimazole. To determine whether or not the metabolic formation of N-OH-AF could lead directly to covalently bound adduct(s) with DNA under these incubation conditions (30 min, pH 7.5), the binding of synthetic and metabolically formed [3H]-N-OH-AF to added calf thymus DNA and to DNA in isolated rat liver nuclei was investigated. In all cases, the amount of DNA-bound carcinogen accounted for 0.08 to 0.15% of the N-OH-AF present in the incubation mixtures. These data, when compared to the levels of AF bound to hepatic nuclear DNA reported in vivo, suggest that the nonenzymatic reaction of N-OH-AF with nuclear DNA may be sufficient to account for a substantial portion of the observed in vivo binding of this carcinogen. (Author abstract) (77 Refs)

27. EVIDENCE FOR A PUTATIVE N-NITROSOPYRROLIDINE-DERIVED DNA ADDUCT (MEETING ABSTRACT)

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Toxicologist; 2(1):68 1982

Many carcinogens, including dialkylnitrosamines, are thought to induce cancer through covalent binding of derivatives to target organ DNA. Some evidence suggests that N-nitrosopyrrolidine (NP) and other cyclic nitrosamines are at variance with this mechanism. Liver DNA was isolated 3, 6, 12, 18, 24, 30, or 36 hr after rats were given 900 mg NP/kg body wt po. The DNA was subjected to neutral thermal hydrolysis in pH 7 buffer for 1 hr at 100 degrees, and hydrolysates were fractionated by strong cation exchange high pressure liquid chromatography. Elution of fractions was monitored by fluorescence spectrophotometry. An unidentified fluorescent material was detected in all DNA hydrolysates from NP-treated rats, but not in hydrolysates from control animals. The putative

adduct formed rapidly; the concentration of this material in liver DNA increased more than 3-fold from 3 to 12 hr following NP treatment, then began to gradually decrease over later times. The fluorescent material did not co-chromatograph with standard guanine derivatives methylated or ethylated in either the 7-or O6-position. The concentration of fluorescent material in liver DNA hydrolysates was dose-dependent in rats killed 12 hr after receiving 14, 28, 57, 113, 225, 450 or 900 mg NP/kg body wt. Neutral thermal hydrolysis is known to release 3-alkyladenine and 7-alkylguanine from DNA; alkylguanines fluoresce well, while alkyladenines do not. Hence, the putative DNA adduct in NP-treated rats may be a guanine derivative substituted in the 7-position. (1 Ref)

28. COVALENT BINDING OF METABOLICALLY ACTIVATED HYDROCARBONS TO SPECIFIC MICROSOMAL PROTEINS.

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Adv Exp Med Biol; 136(partA):341-348 1982

Binding specificity of benzene (BZ), chlorobenzene (CB), 3-methylcholanthrene (MCH), and benzo(a)pyrene (BP) to rat liver microsomal proteins (MP) after metabolic activation was examined. The examined compounds bound covalently to MP in a NADPH-dependent manner indicating that metabolic activation was required for binding. Reduced glutathione inhibited binding. The binding patterns to MP examined by SDS-polyacrylamide gel electrophoresis and fluorography were quite similar for metabolic activated BZ, CB, and phenol. The binding patterns to liver microsomes from phenobarbital (PB)- or MCH-treated rats did not differ significantly from those of control animals. The binding patterns for BP and MCH were distinctly different from those of BZ, phenol, and CB. The binding of these compounds to microsomes from MCH-treated rats was much higher than that to microsomes from control or PB-treated animals. Seven BP metabolites were isolated and incubated with NADPH and microsomes from control or pretreated rats. All isolated metabolites, including BP-4,5-oxide, had to be metabolically activated to bind covalently. Variations were found among the metabolites in extent and specificity of binding. Of the isolated metabolites tested, BP-7,8-dihydrodiol bound most efficiently after metabolic activation, particularly to microsomes from MCH-treated rats. Results suggested that the binding pattern, at least in part, is determined by the mechanism of metabolic activation. (13 Refs)

EFFECT OF CARCINOGENS ON MACROMOLECULAR SYNTHESES

29. ALPHA-FETOPROTEIN SYNTHESIS DURING EARLY STAGES OF HEPATOCARCINOGENESIS IN MICE WITH DIFFERENT SENSITIVITY TO ORTHO-AMINOAZOTOLUENE.

Serova IA, Kaledin VI, Kostyrev OA, Gruntenko EV
Inst. Cytology and Genetics, Novosibirsk, USSR
Dokl Akad Nauk SSSR; 263(5):1245-1249 1982

Alpha-fetoprotein (AFP) synthesis during ortho-aminoazotoluene (OAT) induced liver carcinogenesis was studied in OAT-sensitive DD/He, DBA/2J, CBA/LacSto, and A/He mice and in OAT-resistant CC57BR/Mv and BALB/cLacSto mice. The ip or sc administration of OAT produced marked necrotic changes in the liver of sensitive mice. Resistant mice and sensitive CBA mice did not show morphological changes in the liver tissue. Both sensitive and resistant mice showed the first peak of AFP on day 4 after OAT administration. The resistant mice showed normalization of AFP blood levels, while the sensitive mice developed the second increase of AFP level. (10 Refs) (In RUS)

REVIEWS

30. REACTIVE METABOLITES AS KEY INTERMEDIATES IN PHARMACOLOGIC AND TOXICOLOGIC RESPONSES: EXAMPLES FROM CHEMICAL CARCINOGENESIS.

Miller EC, Miller JA
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Adv Exp Med Biol; 136(partA):1-21 1982

Electrophilic reactants as toxic agents, mechanism of chemical carcinogenesis, and metabolic activation of chemical carcinogens (CC) and of 1'-hydroxyestragole (HE) are discussed. Current data on carcinogenesis indicate that the first stage, initiation, depends on the reaction of a strong electrophilic reactant (ER) with DNA and a resultant mutation of the DNA. The second stage, promotion, requires a prolonged time for completion and appears to be reversible in the early phases. The activation reactions of critical importance in the induction of tumors are influenced by the many factors (molecular geometry, polarity) that determine the approach of the procarcinogen or proximate carcinogen to the enzyme(s), the properties of the enzyme(s) in relation to the particular substrate, and the susceptibility of ER to inactivating reactions before they reach the critical target for the induction of neoplasia. Examples of some reactions for the activation of procarcinogens to ER are summarized and the metabolic activation of a broader range of CC is shown. The characterization of the DNA adducts formed from HE was studied in mouse liver. Co-chromatography in three system showed the apparent identity of the principal products formed in vivo with the principal products formed by reaction of 1'-acetoxyestragole with deoxyguanosine (3 products) and deoxyadenosine (1 product). Data suggested that each of the deoxyguanosine adducts was substituted on the exocyclic amino group. The mutagenic and carcinogenic responses of cells to the attack by chemicals depend on the genes in the DNA that are affected, the susceptibility of the modified nucleic acid residues to repair, the fidelity of the repair, and the effects of unrepaired lesions on DNA replication. (56 Refs)

31. CHEMICAL CARCINOGENESIS: INTERACTIONS OF CARCINOGENS WITH NUCLEIC ACIDS.

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Dept. Pathology, Univ. Toronto, Toronto, Ontario, Canada
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

The nature of modified nucleic acids following interactions with carcinogens is reviewed. Interactions of chemical carcinogens with DNA include covalent interactions such as alkylating agents, nitrosamines and nitrosamides, and noncovalent interactions of both internal and external binding types. Pyridine-N-oxides and many inorganic metal compounds are known to be carcinogenic. The use of fractionation techniques has revealed that carcinogens exhibit a preferential interaction with some regions of DNA in chromatin. Interactions of chemical

carcinogens with RNA have been studied, and alterations in RNA have been attributed to alkylating agents such as nitrosamines and nitrosamides, to urethan, to aromatic amines and amides, and to polycyclic aromatic hydrocarbons. Interactions of carcinogens with nucleic acids exert a profound effect on the structure and synthesis of DNA and RNA, gene expression, and regulation of cellular development. Although the exact mechanism or mechanisms by which DNA damage and repair are involved in carcinogenesis is not completely understood, there is overwhelming evidence indicating a causal relationship between these two processes. (634 Refs)

32. SEQUENTIAL ASPECTS OF CHEMICAL CARCINOGENESIS: SKIN.

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Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

The two-stage hypothesis, the initiation-promotion hypothesis, was based on animal studies of sequential stages of skin carcinogenesis. Initiators for skin carcinogenesis include 2-acetylaminofluorene, UV light, beta-radiation, certain metabolites of 'complete' carcinogens, various alkylating agents and mutagens. Promoters for skin carcinogenesis include physical agents, 'complete' chemical carcinogens, non- or weakly-acting skin carcinogens, croton oil, straight-chain N-alkanes, phenolic compounds, extracts of tobacco leaf, and extracts of tobacco smoke condensates. The two-stage system in skin carcinogenesis has been extended, based on further experiments. Evidence that a mutational change in the DNA genome was responsible for the initiating change of carcinogenesis is based on the ability of most carcinogens to bind with DNA and that there is a fairly good correlation between mutagenic and carcinogenic properties among a wide range of compounds. Evidence for the stimulation of synthetic processes in the cell includes the stimulation of DNA and RNA synthesis as well as protein and phospholipid synthesis. The effects of enzymatic functions in the cell are based on an increase in proteinase activity, on stimulation of ornithine decarboxylase activity, on changes in cyclic nucleotide levels, and on a decrease in histidase activity. (378 Refs)

33. CURRENT CONCEPTS IN ULTRAVIOLET CARCINOGENESIS.

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Proc Soc Exp Biol Med; 170(2):115-125 1982

The pathobiology and epidemiology of UV-induced carcinogenesis are reviewed. The two most common types of nonmelanoma skin cancers in humans and those most related to sun exposure are basal cell carcinoma and squamous cell carcinoma. Nonmelanoma skin cancer in the United States occurs with an incidence of about 400,000 new cases per yr. Phenotypic characteristics associated with the development of this type of cancer include light eye color, fair complexion, and poor tanning ability. While highly pigmented races appear refractory to UV-induced skin carcinogenesis, albinos of such races experience a high incidence of such tumors on sun-exposed areas of the body. Physiologic aging may play a role in the development of nonmelanoma skin cancer. Exposure of human skin to UV radiation results in immediate changes in the nuclear DNA that can be demonstrated with antibodies specific for DNA altered by UV radiation. Modulation of UV-induced skin carcinogenesis by antioxidants, physical factors, carcinogens, retinoids, Beta-carotene, and the immune system are discussed. Malignant melanoma is a neoplasm derived from melanocytes. Both the incidence and death rate from malignant melanoma appear to have been increasing in the past few decades. Although solar exposure appears to be associated with the incidence of melanoma, the relationship is not as clear as for nonmelanoma skin cancer. (128 Refs)

34. CYTOLOGIC AND BIOCHEMICAL GENETIC EFFECTS OF CHEMICAL CARCINOGENS.

Rasmussen RE
Dept. Community and Environmental Medicine, California Univ., Irvine, CA
Cytologic and Biochemical Genetic Effects of Chemical Carcinogens. Available from National Technical Information Service, Springfield, VA, as AD-A107 615/7:, 43 pp., 1981.

The first project is concerned with the relationship between initiation of cancer by chemicals and the damage and repair of DNA in cells and tissues susceptible to the carcinogenic action of the chemicals. The working hypothesis is that interaction of the carcinogen with cellular DNA is a necessary step in carcinogenesis and that this interaction may cause DNA damage which is then followed by DNA repair synthesis. The second project was conducted with the cooperation of the staff of the Toxic Hazards Research Unit at AMRL, WPAFB. Rats and hamsters were exposed by inhalation to hydrazine at 750 ppm for 1 hr. Groups of animals which had been exposed only once or which had been exposed 10 times were shipped to UC Irvine for study. The factors studied were (1) DNA replication in the lung; (2) DNA repair synthesis in the lung; (3) Cellular replication in the lung and nasal turbinates; and (4) Metabolism of a known lung carcinogen, 3H-benzo(a)pyrene, by lung slices from the treated animals. The third project was initiated during the current year with the goal of developing an animal model in which biochemical and cytogenetic factors could be studied during the process of tumorigenesis. Range-finding studies are underway at the Toxic Hazards Research Unit to establish the intratracheal dosage of 3-methylcholanthrene necessary to produce a high yield of lung tumors in Fischer 344 rats within 12 months. (Author abstract)

35. CHEMICAL CARCINOGEN (HYDRAZINE, POLYNUCLEAR HYDROCARBON AND/OR SYNTHETIC JET FUEL COMPONENTS) INDUCED CARCINOGENESIS OF HUMAN CELLS, IN VITRO.

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Chemical Carcinogen (Hydrazine, Polynuclear Hydrocarbon and/or Synthetic Jet Fuel Components) Induced Carcinogenesis of Human Cells, In Vitro. Available from National Technical Information Service, Springfield, VA, as AD-A107 721/3:, 127 pp., 1981.

Select chemicals of interest to the Air Force and identified as man made environmental contaminants have been found to neoplastically transform human cells in vitro. Benzo(a)pyrene one of these compounds of interest, exhibits unique features of movement from the extracellular environment to the nucleus of the cell. B(a)P is transported into human foreskin fibroblasts from the plasma membrane to the nucleus by binding as the unmetabolized parent B(a)P. B(a)P forms a low binding association with a lipoprotein complex in the cytoplasm that has a mol wt of 12,500. The B(a)P following penetration into the nucleus is then oxygenated to various metabolites. Benzopyrene-diol-epoxide-1 has been identified as a metabolite in the nucleus that interacts with deoxy-guanine to form a DNA adduct, 7R-BPDE-I-dG. We then used another hydrocarbon 1,2,3,4-tetra-

hydro-7,12-dimethyl benz(a)anthracene to induce carcinogenesis in human cells. To date we have no evidence for extracellular or intracellular metabolism of this compound under conditions for transformation. We conclude tentatively that this data suggests that there is an alternate requirement for polynuclear hydrocarbon induced carcinogenesis in human cells compared to rodent cells. (Author abstract)

36. REPAIR OF RADIATION DAMAGE IN MAMMALIAN CELLS.

Setlow RB
Brookhaven Natl. Lab., Upton, NY
Repair of Radiation Damage in Mammalian Cells. Available from National Technical Information Service, Springfield, VA, as DE81030824:, 16 pp., 1981.

The responses, such as survival, mutation, and carcinogenesis, of mammalian cells and tissues to radiation are dependent not only on the magnitude of the damage to macromolecular structures - DNA, RNA, protein, and membranes - but on the rates of macromolecular syntheses of cells relative to the half-lives of the damages. Cells possess a number of mechanisms for repairing damage to DNA. If the repair systems are rapid and error free, cells can tolerate much larger doses than if repair is slow or error prone. It is important to understand the effects of radiation and the repair of radiation damage because there exist reasonable amounts of epidemiological data that permits the construction of dose-response curves for humans. The shapes of such curves or the magnitude of the response will depend on repair. Radiation damage is emphasized because: (a) radiation dosimetry, with all its uncertainties for populations, is excellent compared to chemical dosimetry; (b) a number of cancer-prone diseases are known in which there are defects in DNA repair and radiation results in more chromosomal damage in cells from such individuals than in cells from normal individuals; (c) in some cases, specific radiation products in DNA have been correlated with biological effects, and (d) many chemical effects seem to mimic radiation effects. A further reason for emphasizing damage to DNA is the wealth of experimental evidence indicating that damages to DNA can be initiating events in carcinogenesis. (Author abstract)

37. RECENT DEVELOPMENTS IN THE MECHANISMS OF DNA REPAIR AND IN THE ROLE OF DNA REPAIR IN CHEMICAL CARCINOGENESIS AND CANCER CHEMOTHERAPY.

Roberts JJ
Inst. Cancer Res., Royal Cancer Hosp., Pollards Wood Res. Station, Chalfont St. Giles, Bucks., HP8 4SP, England
Adv Exp Med Biol; 136(partB):1367-1387 1982

Mechanisms of DNA repair, including excision repair, and the role of DNA repair in chemical carcinogenesis and cancer chemotherapy are discussed. Base excision (small patch repair) and nucleotide excision (large patch repair) are described and a two-step model for excision repair of pyrimidine dimers is illustrated. Whether any specific excision repair enzyme acts similarly on UV- and chemically-induced DNA damage to remove a modified base by glycosylase action is unproven. Inducible excision repair processes in prokaryotic cells (adaptation and SOS repair) and in mammalian cells is discussed. Reactivity of compounds can be correlated with mutagenicity and carcinogenicity: agents that react by a unimolecular substitution reaction (SN1) are the most potent mutagens and the most potent carcinogens. SN1 reactivity in turn correlates with the ability of compounds to react more extensively with the oxygen atom sites in DNA. The physiological state of a tissue determines not only the degree of cell proliferation taking place, but also the cytotoxic effect of DNA lesions that modify or act as a block to DNA replication. DNA excision repair and cytotoxicity is discussed. Normal cells may be proficient in repair of alkylation damage, while tumor strains may be either proficient or deficient in repair. Replication of DNA on a damaged template (RDT), or post-replication repair, occurs when unexcised DNA damage is circumvented during replication. In rodent cells, RDT may be adversely influenced by post-treatment incubation in the presence of caffeine. RDT may occur by gapped synthesis or replicative bypass (branch migration). Base mispairing and the introduction of potentially mutagenic lesions has been implicated in the etiology of nitrosamine-induced carcinogenesis. (68 Refs)

38. LACK OF INDUCTION OF SINGLE-STRAND BREAKS IN MAMMALIAN CELLS BY SODIUM AZIDE AND ITS PROXIMAL MUTAGEN.

Arenaz P, Nilan RA, Kleinhofs A
Washington State Univ., Coll. Agriculture, Pullman, WA
Lack of Induction of Single-Strand Breaks in Mammalian Cells by Sodium Azide and Its Proximal Mutagen. Available from National Technical Information Service, Springfield, VA, as DE82001721:, 19 pp., 1981.

The mutagenicity of sodium azide in both higher plants and bacteria is well documented. However, in mammalian cells, research on the effects of azide on gene mutations has produced conflicting results. Furthermore, no research has been conducted on the effects of azide and its proximal mutagen (mutagenic metabolite) on single strand breaks. The experiments herein were designed to overcome this lack of information on azide mutagenicity and to evaluate the potential hazard of azide exposure to man. Chinese hamster V79 cells were treated with either azide or its proximal mutagen(s) for 2 hr or 6 hr respectively and analyzed by alkaline elution for single-strand breaks. The data showed that there was no effect of either azide or the proximal mutagen(s) on single-strand DNA breaks nor was there any indication that azide or the proximal mutagen(s) induced DNA-protein crosslinks. The data suggest that neither azide nor its proximal mutagen(s) interact directly with DNA and suggest that the methods may be applied to any specified population and dose scenario. (Author abstract)

39. CONSTITUTIVE AND CARCINOGEN-DERIVED DNA BINDING AS A BASIS FOR THE ASSESSMENT OF POTENCY OF CHEMICAL CARCINOGENS.

Lutz WK
Inst. Toxicology, ETH, Univ. Zurich, CH-8603 Schwerzenbach, Switzerland
Adv Exp Med Biol; 136(partB):1349-1365 1982

The hypothesis that ground-level DNA damage is unavoidable and must be regarded as constitutive to a cell is presented. Sources for this type of damage include physiological reactive intermediates, nitrosamines, irradiation, carcinogenic metals, and viruses. Carcinogens are classified as initiating (DNA damaging, genotoxic) and nongenotoxic (act by modulating reactions and side reactions that increase or constitutive DNA damage or enhance the chance for such damage to proceed to a tumor). Carcinogenic potency of a carcinogen is defined as a product of persistent DNA damage x mutagenicity x nongenotoxic modulation of DNA damage. A correlation of DNA binding in vivo and the form of a 'Covalent Binding Index' (CBI) to the carcinogenic potency is shown. The CBI equals (micromole chemical bound/mole DNA nucleotides)/(millimole chemical administered/kg animal wt). Good linear corre-

lation was found with an approx uncertainty of the estimate of a factor of 10 with a total span of values of 10(6). DNA binding is not enough to describe the potency of carcinogens; additional information is necessary to assess the organ specificity of initiating carcinogens. When administered alone, the nongenotoxic carcinogens appear to be much less potent than initiating carcinogens. Nongenotoxic carcinogens cannot be detected on the basis of chemical structure and short-term tests of their carcinogenic potency are not available. (21 Refs)

40. THE ACTIVATING ROLE OF GLUTATHIONE IN THE MUTAGENICITY OF 1,2-DIBROMOETHANE.

van Bladeren PJ, Breimer DD, Rotteveel-Smijs GM, Hoogeterp JJ, Mohn GR, De Groot A, Van Zeeland AA, Van der Gen A
Dept. Pharmacology, Univ. Leiden, P.O. Box 9502, 2300 RA Leiden, The Netherlands
Adv Exp Med Biol; 136(partA):809-820 1982

Role of conjugation to glutathione (GSH) in the mutagenicity of 1,2-dibromoethane (DBE) was investigated and some preliminary results on the occurrence of reactive GSH conjugates in vivo are reported. The activity of GSH-S-transferase in vitro, synthesis and reactions of model conjugates, mutagenicity of DBE, and DNA binding of DBE are reviewed. DBE was tested to determine which mechanism is responsible for the activation. Results indicated that the enhancement of mutagenic activity is caused by conjugation to GSH. The spontaneous binding of DBE to DNA may result from initial reactions with sulfur or nitrogen nucleophiles, giving rise to the same type of half-mustards as the GSH conjugates. Rats excreted 30-50% of DBE in the form of mercapturic acid. Direct conjugation of GSH with DBE and DBE oxidation followed by loss of hydrogen bromide may lead to the structure of the metabolite. Excretion of N-acetyl-S-2-hydroxyethyl-L-cysteine by male Wistar rats after administration of 0.1 millimole DBE/rat with and without pretreatment with 10 g 1-phenylimidazole/rat is presented. Results show that direct conjugation of DBE to GSH and thus formation of the reactive 2-halogenothioether in vivo is a viable pathway of metabolization. Conjugation to GSH can give rise to the formation of reactive glutathione conjugates, provided a second leaving group is present at the carbon atom next to the one where sulfur substituent becomes attached. (21 Refs)

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CHEMICAL CARCINOGENESIS

1. TOXICITY OF POLYBROMINATED BIPHENYLS (PBBS) IN DOMESTIC AND LABORATORY ANIMALS.

Damstra T, Jurgelski W, Posner HS, Vouk VB, Bernheim NJ, Guthrie J, Luster M, Falk HL
Natl. Inst. Environmental Health Sciences, Post Office Box 12233, Research Triangle Park, NC, 22709
Environ Health Perspect; 44():175-188 1982

2. CHLOROFORM: A REVIEW OF ITS METABOLISM, TERATOGENIC, MUTAGENIC, AND CARCINOGENIC POTENTIAL.

Davidson IW, Sumner DD, Parker JC
(c/o Parker) ECAO, Environmental Protection Agency, MD-52, Research Triangle Park, MD, 27711
Drug Chem Toxicol; 5(1):1-87 1982

3. FORMALDEHYDE IN PRESENT-DAY ENVIRONMENTAL TOXICOLOGY.

Beritic T, Kovac S, Dinov D
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Arh Hig Rada Toksikol; 32(4):363-395 1981
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4. HORMONES AS ETIOLOGICAL AGENTS IN NEOPLASIA.

Furth J
Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

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Cattedra di Endocrinologia, Universita di Torino, C.so Polonia, 14, 10126 Turin, Italy
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Institut fur Arbeits- und Sozialmedizin, Poliklinik fur Berufskrankheiten, Universitat Erlangen-Nurnberg, Schillerstrasse 25-29, D-8520 Erlangen, W. Germany
Zentralbl Bakteriol Mikrobiol Hyg [B]; 173(1/2):63-91 1981
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Am J Public Health; 72(6):585-588 1982

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12. RADIOBIOLOGY OF RISK ESTIMATES IN MEDICAL IRRADIATION (MEETING ABSTRACT)

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IN: 148th National Meeting of the American Association for the Advancement of Science, January 3-8, 1982, Washington, D.C American Association for the Advancement of Science 182 pp., 1982.

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Drug Chem Toxicol; 4(4):311-329 1981

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Dept. Epidemiology, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

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Louisiana State Univ. Medical Center, New Orleans, LA, 70112
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Juchau MR, Chao ST, Namkung MJ

Dept. Pharmacology, Sch. Medicine, SJ-30, Univ. Washington, Seattle, WA, 98195

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MODIFICATION OF CARCINOGENESIS

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43. THE ONCOGENIC CIRCLE CLOSES.

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Lab. Government Chemist, London, England

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ICRDB CANCERGRAM

MECHANISMS OF CARCINOGENESIS

Macromolecular Alteration and Repair

SERIES CK11 No. 82/11

NOVEMBER, 1982

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BIOLOGICAL ASPECTS OF DNA ALTERATION AND REPAIR IN RELATION TO CARCINOGENICITY

1. ORGAN SITE SPECIFICITY FOR CANCER IN CHROMOSOMAL INSTABILITY DISORDERS.

Feinberg AP, Coffey DS
(c/o Coffey) Oncology Center, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205
Cancer Res; 42(8):3252-3254 1982

DNA rearrangement rather than point mutation is an emerging hypothesis for human carcinogenesis. Although there is no direct evidence for this hypothesis, indirect evidence is provided by cancer cytogenetics and genetics. It has been suggested that patients with Bloom's syndrome, a disorder of spontaneous chromosomal rearrangement, develop the common fatal internal cancers and thus that genetic rearrangements, rather than chemical mutagens, cause most internal human cancers. To test this observation, we have derived age- and sex-adjusted cancer incidence rate ratios for specific organ sites in patients with three chromosomal instability disorders (Bloom's syndrome, xeroderma pigmentosum, and dyskeratosis congenita)

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and have found that the increased incidence of cancer in all three disorders limited to specific and often uncommon organ sites. We conclude that chromosomal instability disorders do not predispose patients to the common fatal internal cancers. Although DNA rearrangement remains a promising concept in human carcinogenesis, the organ site specificity of cancers associated with Bloom's syndrome, xeroderma pigmentosum, and dyskeratosis congenita cannot be used as evidence to implicate this mechanism. (Author abstract) (37 Refs)

2. DNA-REPAIR SYNTHESIS IN BLAST CELLS FROM PATIENTS WITH ACUTE MYELOBLASTIC LEUKAEMIA.

Lewensohn R, Ringborg U

Radiumhemmet, Karolinska Hosp., S-401 01 Stockholm, Sweden

Scand J Haematol; 28(5):399-407 1982

DNA-repair synthesis was studied in blast cells from patients with acute myeloblastic leukemia. The DNA-repair synthesis, measured as 3H-thymidine incorporation, was registered as unscheduled DNA synthesis by autoradiography, and also after suppression of the replicative DNA synthesis by hydroxyurea by liquid scintillation. There was good correlation when results from both methods were compared. A significantly wider variation of unscheduled DNA synthesis was found in leukemic as compared to normal blast cell populations. There was also a wider variation within individual leukemic blast cell samples compared to normal samples. A correlation was found between unscheduled DNA synthesis induced by nitrogen mustard and by UV-irradiation in the leukemic blast cell populations. The UV-induced unscheduled DNA synthesis in some of the leukemic blast cell populations continued to increase at doses of UV-irradiation at which normal myeloblasts had reached their max level of unscheduled DNA synthesis. This indicates that at least some malignant blast cell populations may possess an effective DNA-repair system. (Author abstract) (21 Refs)

3. UV-REPAIR IS IMPAIRED IN FIBROBLASTS FROM PATIENTS WITH FANCONI'S ANEMIA.

Schwaiger H, Hirsch-Kauffmann M, Schweiger M

(c/o M. Schweiger) Abteilung Biochemische Humangenetik, Institut fur Medizinische Biologie und Genetik, Universitat Innsbruck, A-6020 Innsbruck, Austria

MGG; 185(3):454-456 1982

Fanconi's anemia, a hereditary autosomal disease with chromosomal instability, elevated incidence of cancer and clinical symptoms is accompanied by a DNA repair deficiency. Fibroblasts from patients with Fanconi's anemia were found to be impaired in the DNA repair of UV damage. Nucleoid decondensation and recondensation after UV irradiation were less efficient in fibroblasts from patients with Fanconi's anemia than in those from a healthy proband. These data confirm our earlier findings that DNA ligase is deficient in Fanconi's anemia. (Author abstract) (12 Refs)

BIOLOGICAL ASPECTS OF DNA ALTERATION AND REPAIR IN RELATION TO MUTAGENICITY

4. EXTENT OF EXCISION REPAIR BEFORE DNA SYNTHESIS DETERMINES THE MUTAGENIC BUT NOT THE LETHAL EFFECT OF UV RADIATION.

Konze-Thomas B, Hazard RM, Maher VM, McCormick JJ

(c/o Maher) Carcinogenesis Lab.-Fee Hall, Michigan State Univ., East Lansing, MI, 48824

Mutat Res; 94(2):421-434 1982

Predictions that excision repair-proficient cells treated just prior to S will be significantly more sensitive to the cytotoxic and/or mutagenic effect than will be cells exposed many hr prior to S and that cells which are incapable of excision repair will show no difference in sensitivity were tested. Results obtained with UV radiation as the DNA-damaging agent indicated that semi-conservative DNA synthesis is indeed, the 'critical cellular event' responsible for mutation induction. However, the cytotoxic effect of the agent was not significantly increased in normal fibroblasts treated just prior to S phase, even though the cells' excision repair capacity was critical in determining the survival level ultimately attained. (26 Refs)

5. EFFECTS OF RIFAMPIN ON THE LETHALITY AND THE MUTATION FREQUENCY OF ULTRAVIOLET-IRRADIATED CHINESE HAMSTER V79 CELLS.

Shinohara K

Dept. Radiation Biophysics, Sch. Medicine, Kobe Univ., Kusunoki-cho, Chuo-ku, Kobe-shi, Hyogo 650, Japan

Mutat Res; 94(2):393-396 1982

Effects of rifampin (RF) on UV-irradiated Chinese hamster 79 cells were studied to find out whether a RF-sensitive process exists in mammalian cells as in Escherichia coli. Post-treatment with RF (100 ug/ml) for 24 hr increased the lethality of UV-irradiated V79 cells. D0 and n were 4.3 Joule/square meter (J/m2) and 4.7 for untreated cells, and 3.2 J/m2 and 3.5 for RF-treated cells respectively. The treatment with RF (100 ug/ml) alone for 24 hr had little effect on the lethality of unirradiated cells, as shown by the cloning efficiency of 97.1 +- 13.4% of the control. Treatment with RF at a concentration as low as 20 ug/ml for the whole period of incubation (8 days), or treatment with RF at a concentration greater than 200 ug/ml for 24 hr decreased the colony-forming ability of unirradiated V79 cells to less than 50% of the control. No decrease in the survival of UV-irradiated V79 cells was produced by treatment with RF (up to 500 ug/ml) for 2 hr prior to UV-irradiation. Results indicated that RF might inhibit the inducible repair responsible for survival by a specific inhibition of the production of a protein similar to protein X in E coli even though RF is much less effective in inhibiting eukaryotic RNA polymerase. Post-treatment with RF (100 ug/ml) for 24 hr immediately after UV-irradiation, which increased lethality to V79 cells, did not change the UV-induced mutation frequency. (17 Refs)

6. RELATIONSHIP BETWEEN EXCISION REPAIR AND THE CYTOTOXIC AND MUTAGENIC EFFECT OF THE 'ANTI' 7,8-DIOL-9,10-EPOXIDE OF BENZO[A]PYRENE IN HUMAN CELLS.

Yang LL, Maher VM, McCormick JJ
(c/o Maher) Carcinogenesis Lab.-Fee Hall, Michigan State Univ., East Lansing, MI, 48824
Mutat Res; 94(2):435-447 1982

Effects of the anti isomer of 7,8-diol-9,10-epoxide of benzo[a]pyrene (anti BPDE) were studied in xeroderma pigmentosum XP12BE and normally excising diploid human cells (NF). To determine if the time available for excision repair prior to onset of semi-conservative DNA replication plays a significant role in decreasing the potentially mutagenic effect of anti BPDE, NF cells were synchronized by density inhibition, released, and treated at expression densities from a common stock soln of tritiated anti BPDE approx 16 or 1 hr prior to onset of S. The NF cells treated in situ just prior to S exhibited the highest frequency of induced mutations. The frequencies observed in NF cells treated in situ in early G1 approx 16 hr prior to S or treated in density-inhibited G0 state were significantly (12-to 16-fold) lower than those of NF cells treated just prior to S. No such difference was observed in the excision repair-deficient XP12BE cells. Results supported the hypothesis that the number of DNA lesions remaining unexcised during S determines the mutagenic effect of the agent. Results indicated that DNA replication occurred on templates containing unexcised residues and that the number of anti BPDE adducts remaining unexcised was approx the same in the replicated and the non-replicated fraction of parental DNA. At the onset of S, the number remaining bound in NF cells was approx 2.5 residues/10(6) nucleotides. (14 Refs)

7. DIFFERENTIAL KILLING AND MUTATION INDUCTION BY ULTRAVIOLET LIGHT OR BENZ(A)PYRENE-4,5-OXIDE BY A UV-RESISTANT CLONE OF CHO-K1 HAVING NORMAL REPAIR ABILITY (MEETING ABSTRACT).

Newman CN
Battelle Pacific Northwest Laboratory, Richland, WA, 99352
Proc Am Assoc Cancer Res; 23:194 1982

An ultraviolet light (UV) resistant line of CHO cells, Mut8-16, was examined and its properties compared to its parent, CHO-K1, following treatment with either UV or the active carcinogen benzo(a)pyrene-4,5-oxide (BP-4,5-0). Survival curves obtained after treatment with UV demonstrated a significantly enlarged shoulder in the mutant compared to CHO-K1, though the slopes of the exponential regions of such curves were identical for the two lines. In spite of the dissimilar survival responses, mutation frequencies (to 6-thioguanine) per UV fluence were indistinguishable. Thus, a differential plot of mutation frequency vs survival indicated an enhanced mutability in the mutant, though at high survival UV fluences only; at lower survival levels such differences were little evident. No significant differences in either excision-repair, replication-repair or postreplication-repair following UV were observed. The mutant and parent showed equal sensitivity to the killing effects of BP-4,5-0 though mutation frequencies in this instance were different. Initial mutation rates at low (less than 6uM) concentrations of carcinogen were lower in the mutant. As the concentration of carcinogen was increased, the mutation frequency responses converged with one another. (no Refs)

8. MUTAGENIC RESPONSES OF FIVE INDEPENDENT GENETIC LOCI IN CHO CELLS TO A VARIETY OF MUTAGENS. DEVELOPMENT AND CHARACTERISTICS OF A MUTAGEN SCREENING SYSTEM BASED ON SELECTION FOR MULTIPLE DRUG-RESISTANT MARKERS.

Gupta RS, Singh B
Dept. Biochemistry, McMaster Univ., Hamilton L8N 3Z5, Canada
Mutat Res; 94(2):449-466 1982

Response of several well characterized genetic markers such as those involving resistance to thioguanine, emetine, ouabain, 5-6-dichlororibofuranosylbenzimidazole, and methylglyoxal bisguanylhydrazone towards a number of direct- and indirect-acting mutagens was assessed in proline-requiring Chinese hamster ovary (CHO) cell line. Direct-acting alkylating and DNA-adduct forming agents such as beta-propiolactone, ethyleneimine, N-nitrosomethylurea, 4-nitroquinoline-N-oxide, methyl methanesulfonate, and ethyl methanesulfonate; DNA intercalating and cross-linking agents such as ICR-170, acridine orange, ethidium bromide, mitomycin C, and actinomycin D; and chemicals requiring microsomal activation in other systems such as benzo[a]pyrene, 7,12-dimethylbenz[a]anthracene, benzidine, and beta-naphthylamine were examined. The response of various agents was determined at only two or three concentrations which should have resulted in between 10-80% cell killing. Mutation frequencies of different genetic markers which were observed in the control and mutagen-treated cultures, as well as the mutagenesis significance ratio of various markers, which provide a measure of their relative mutagenic response are shown. Of the genetic loci, no one single locus showed higher response to all of the chemicals, instead, depending upon the chemical, specific loci were found to be more responsive than others. Results indicated that CHO cells possess significant capacity for the metabolic activation of many procarcinogens, and also underscore the merits of measuring the mutagenic response at multiple genetic loci in mutagen screening studies. (40 Refs)

9. MUTAGENESIS BASED ON DEPURINATION BY CHEMICAL CARCINOGENS (MEETING ABSTRACT).

Loeb LA, Schaaper RM, Kunkel TA
Gottstein Memorial Cancer Research Laboratory, SM-30, University of Washington, Seattle, WA, 98195
Proc Am Assoc Cancer Res; 23:254 1982

An analysis of apurinic sites as an intermediate in mutagenesis by chemical carcinogens has been carried out. Alkylation of the N-3 and N-7 positions on purines in DNA causes cleavage of the bond between the base and sugar yielding apurinic sites. Copying of DNA containing apurinic sites by DNA polymerases in vitro results in enhanced mis-incorporations. Transfection of phix174 DNA containing apurinic sites results in mutagenesis when assayed in Escherichia coli spheroplasts expressing error-prone DNA repair. We measured the infectivity and mutagenicity of phix DNA treated with beta-propiolactone (BPL), benzo(a)pyrene diolepoxide, and N-acetoxy acetylaminofluorene. With each compound, mutagenicity is dependent on the induction of the error-prone pathway. Heating of DNA treated with BPL causes alkaline labile (presumably apurinic) sites and concomitantly an increase in mutagenicity. The reversion frequency of untreated amber 86 DNA is 12 X 10(-6), after treatment with BPL it increases to 25 X 10(-6) and exposure of the BPL treated DNA to elevated temperature results in a further increase to 185 X 10(-6). The increase in mutagenicity is proportional to the number of alkaline labile sites intro-

duced and is in agreement with the mutagenic potential of apurinic sites. These results suggest a model in which bulky adducts terminate DNA replication and induce alterations in the DNA replicating complex. (no Refs)

10. MUTATIONAL SPECIFICITY OF UV LIGHT IN ESCHERICHIA COLI: INDICATIONS FOR A ROLE OF DNA SECONDARY STRUCTURE.

Todd PA, Glickman BW
(c/o Glickman) Lab. Molecular Genetics, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709
Proc Natl Acad Sci USA; 79(13):4123-4127 1982

We used the lacI forward mutagenesis system to determine the mutational specificity of UV-induced mutation in a repair-proficient (Uvr+) and a repair-deficient (deltaUvrB) strain of Escherichia coli. The spectra recovered at similar levels of mutagenesis were similar, the exception being a mutational hotspot at site A24 specific to the deltaUvrB strain. Mutations induced at this hotspot, as well as those induced at other mutational hotspots that were found to be common to both the Uvr+ and Uvr- strains, involve G-C to A-T transitions. All of the hotspots are at sites of potential dipyrimidine photoproducts, such as thymine-cytosine and cytosine-cytosine dimers, or of pyrimidine-cytosine photo-product Py-C* lesions. Each of these hotspots occurs at a site in the potential hairpin loop of quasi-palindromic sequences. These observations suggest an important role for DNA structure in determining the fate of UV-induced premutational lesions. (Author abstract) (38 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN VERTEBRATES

11. CELL SPECIFICITY IN HEPATOCARCINOGENESIS: PREFERENTIAL ACCUMULATION OF O(6)-METHYLGUANINE IN TARGET CELL DNA DURING CONTINUOUS EXPOSURE OF RATS TO 1,2-DIMETHYLHYDRAZINE.

Bedell MA, Lewis JG, Billings K C, Swenberg JA
Dept. Pathology, Chemical Industry Inst. Toxicology, Research Triangle Park, NC, 27709
Cancer Res; 42(8):3079-3083 1982

Concentrations of the major methylated DNA purines were determined in two liver cell populations of Fischer 344 rats during administration of 30 ppm 1,2-dimethylhydrazine (SDMH) in the drinking water for periods of up to 4 wk. Quantitation of 7-methylguanine and O6-methylguanine (O6MG) was achieved by highly sensitive optical methods following separation of DNA bases by high-performance liquid chromatography. Overall alkylation as indicated by the concentration of 7-methylguanine was near max in both hepatocytes and liver nonparenchymal cells by the third day of SDMH administration. Similar amounts of 7-methylguanine were present in the two liver cell populations at seven of nine time points during 4 wk of exposure. In contrast, dramatic differences in the cumulative concentrations of O6MG were seen in the two cell populations. Nonparenchymal cells accumulated O6MG during the first 8 days of exposure and had up to a 30-fold greater concentration of this product than did the corresponding hepatocytes. In the hepatocytes, a rapid decline in O6MG concentration was observed between 1 and 3 days of exposure to SDMH. Thereafter, only low levels of this promutagenic lesion were present in hepatocytes. Exposure of rats to the same regimen of SDMH for up to 10 mo caused angiosarcomas in the livers of over 90% of the animals, while hepatocellular carcinomas occurred in only 40%. Thus, a strong correlation exists between the inability to repair O6MG and cell specificity for carcinogenesis. (Author abstract) (50 Refs)

12. LIMITED REMOVAL OF O6-METHYLGUANINE IN SYRIAN HAMSTER EMBRYO CELLS BY CONCENTRATIONS OF METHYLATING CARCINOGENS THAT INDUCE TRANSFORMATION (MEETING ABSTRACT).

Doniger J, Day R, DiPaolo J
Laboratories of Biology and Molecular Carcinogenesis, National Cancer Institute, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:292 1982

Excision repair of methylated bases, lethality, host cell reactivation of adenovirus, and neoplastic transformation were studied with Syrian hamster embryo cells (HEC) treated for 1 hr with either N-methyl-N'-nitro-N-nitroso-guanidine (MNNG) or methylnitrosourea (MNU). Transformation and survival were analyzed in a 7 day colony assay. DNA, isolated from confluent cultures treated with 3H-methyl-carcinogen, was acid hydrolized. 3H-methylated bases and total guanine were analyzed using reverse phase high pressure liquid chromatography. Equitoxic doses (55-60% survival) of MNNG (.4 ug/ml) or MNU (20 ug/ml) induce 1.7-1.8% transformation. No transformation was observed in non-treated cultures. Furthermore, equitoxic doses (85-90% survival) of MNNG (.25 ug/ml) or MNU (10 ug/ml) produced the same level of N7-and O6-methylguanine adducts after 1 hr treatment. When HEC were incubated for 24 hr post MNNG or MNU the level of both N7-and O6-methylguanine per mol guanine was reduced by about one half. Thus HEC have a limited capacity to repair both of these adducts. The survival of MNNG treated adenovirus plaqued on confluent non-treated HEC monolayers was intermediate compared to survival on mer+ or mer- human cells. Mer- cells lack the ability to repair O6-methylguanine. The persistence of O6-methylguanine in MNNG or MNU treated HEC is consistent with the hypothesis that this lesion is relevant to induction of carcinogenesis. (no Refs)

13. REMOVAL FROM DNA OF O6-METHYLGUANINE (O6-MEG) BY HUMAN LIVER FRACTIONS (MEETING ABSTRACT).

Montesano R, Bresil H, Likhachev A, Von Bahr C, Roberfroid M, Pegg AE
International Agency for Research on Cancer, Lyon, France
Proc Am Assoc Cancer Res; 23:44 1982

Among the various DNA adducts formed by methylating agents, O6-meG has been implicated both in mutagenesis and carcinogenesis. The removal from DNA of this adduct is carried out by a DNA repair system which is distinct from those responsible for the removal of other DNA adducts, like 3-methyladenine or 7-methylguanine. In this study we have used an in vitro assay to measure the capacity of human liver fractions to catalyze the removal of O6-meG from DNA. Liver fractions of ten human beings were obtained from kidney transplant donors, who had total cerebral infarction, and were frozen and stored at-80 C. These samples were processed in a manner known to isolate the O6-meG removal system and the activity compared with that obtained from rat liver fractions over a range of protein concentrations. After a 60 min incubation the tritium labelled DNA was precipitated and the amounts of O6-and 7-methylguanine determined by Sephadex

G10 chromatography in the acid hydrolysate. The ten different human liver samples had similar activities and less than 1 mg of protein was needed to remove more than 50% of the O6-meG from the DNA substrate, reaching more than 92% with 6.25 mg. With rat liver fraction prepared in the same way, about 70% of the O6-meG was removed with 12.5 mg of protein. The results, based on measurements in which less than 60% of the Substrate was removed, show that the human liver fractions were about 10 times more active than the rat liver fractions. No such difference was observed in the rate of loss of 7-methylguanine. (no Refs)

14. RELATIONSHIP BETWEEN SPECIFIC DNA BASE METHYLATION AND INDUCTION OF CYTOTOXICITY, SISTER-CHROMATID EXCHANGES AND CHROMOSOME ABERRATIONS IN CHINESE HAMSTER CELLS (MEETING ABSTRACT).

Medcalf AS, Connell JR
Michigan State University, East Lansing, MI, 48824
Proc Am Assoc Cancer Res; 23:256 1982

An investigation into the relationship between specific DNA purine methylation and induction of cytotoxicity, sister-chromatid exchanges (SCE) and chromosome aberrations in Chinese hamsters cells (V79) was carried out. Density-inhibited cells were treated with either N-[14C] methyl-N-nitrosourea (MNUA) or [14C] dimethyl sulphate (DMS) and then incubated in the density-inhibited state for various times before being assayed for the three biological end-points. At equitoxic doses of MNUA and DMS, we observed similar SCE frequencies and similar chromosome aberration frequencies. However, MNUA reacted to a far greater extent than DMS at the O-6 atom of guanine, while both agents produced similar levels of 3-meA (methyladenine) and similar levels of 7-meG (methylguanine). Colony-forming ability, as a function of incubation time, was inversely correlated with 3-meA levels in DNA, particularly during the initial 4-8 hr of post-methylation incubation. A decrease in SCE frequency was observed during incubation after treatment, but no significant variation in chromosome aberration frequency was discernable with length of incubation. The results suggest that monofunctional methylating-agent induced cytotoxicity, SCEs and chromosome aberrations are not primarily a consequence of O6-meG formation in DNA and that cytotoxicity and SCE induction may be more dependent on methylation of the N-3 atom of adenine. No specific adduct could be correlated with induction of chromosome aberrations. (no Refs)

15. THE INFLUENCE OF ASBESTOS ON THE FORMATION AND REMOVAL OF BENZO(A)PYRENE-DNA ADDUCTS IN A HAMSTER TRACHEAL EPITHELIAL CELL LINE (MEETING ABSTRACT).

Eastman A, Mossman BT, Bresnick E
Department of Biochemistry and Pathology, University of Vermont College of Medicine, Burlington, VT, 05405
Proc Am Assoc Cancer Res; 23:236 1982

The effect of asbestos fibers (crocidolite and chrysotile) on the interaction of benzo(a)pyrene (BP) with a hamster tracheal epithelial cell line (HTE-B) has been investigated. When BP alone was incubated with HTE-B cells, 50% of the applied hydrocarbon was recovered as water soluble metabolites at 8 hr while 5% was recovered as intracellular unmetabolized BP. After 8 hr incubation with BP, the medium was replaced and a 50% reduction in alkylation was observed in 24 hr with about 80% removed by 5 days. High performance liquid chromatography separation of the DNA adducts demonstrated six adducts. Of these six adducts, two were rapidly removed while two were relatively poorly removed during the 5 day repair period. In comparative studies, BP was coated onto asbestos and applied to HTE-B cells. An enhanced uptake was observed with 80% BP associated with the cells after 1 hr. Metabolism was only slightly inhibited as compared to experiments without asbestos but at 8 hr nearly 50% of the applied hydrocarbon was retained by the cells in unmetabolized form. Analysis of repair was complicated by continued formation of alkylated products in DNA after removal of BP. However, after 24 hr post-treatment, only 5% of the applied BP remained in the cells. At 5 days, it appeared that removal of DNA-bound adducts was inhibited. Experiments with both crocidolite and chrysotile gave the same results. It is concluded that the cocarcinogenic effect of asbestos may be due to enhanced cellular uptake of BP as well as inhibition of subsequent DNA repair. (no Refs)

16. DIFFERENTIAL RATE OF IN VIVO DNA REPAIR SYNTHESIS IN LUNG AND LIVER OF MICE FOLLOWING BENZO(A)PYRENE (BP) TREATMENT (MEETING ABSTRACT).

Kulkarni MS, Angerman-Stewart J, Anderson MW
National Institute of Environmental Health Sciences/National Institute of Health, Research Triangle Park, NC, 27709
Proc Am Assoc Cancer Res; 23:255 1982

A/HeJ mice are susceptible to BP-induced pulmonary neoplasia, whereas the liver is resistant to it. We have previously demonstrated that the formation and disappearance of BP-DNA adducts in A/HeJ mice in vivo are similar in lung and liver. In the present investigations, BP-induced unscheduled DNA synthesis (UDS) was examined in vivo in lung and liver of A/HeJ mice. Following BP treatment, 3H-thymidine incorporation was measured using hydroxyapatite column chromatography and trichloroacetic acid (TCA) precipitation of phenol-extracted DNA, and also by autoradiography. Mice were given BP (po 0.3 mg per mouse) by gavage, and two hours prior to sacrifice 3H-thymidine was administered by ip. DNA replication was differentiated by total DNA repair synthesis by the use of hydroxyurea (HU). Animals were sacrificed at different time points from 4-72 hours following BP dose. Replication and UDS were measured by DPM/mg total DNA. We found in reproducible experiments that BP caused minimum or no UDS in lung where as in liver UDS was significant at all time points examined (ie, approx 3,000 dpm/mg DNA at 24 hours). DNA synthesis and UDS were further differentiated by in vivo autoradiography. Autoradiographs of one micron thick lung and liver tissues support the above data. These different rates of DNA repair synthesis could be one of the factors for tissue-susceptibility to BP-induced neoplasia. (no Refs)

17. DETECTION OF DNA INTERACTION WITH BIS(CHLOROMETHYL)ETHER AND FORMALDEHYDE IN EPITHELIAL CELLS BY USE OF S-1 NUCLEASE (MEETING ABSTRACT).

Belman S, Garte SJ
Department of Environmental Medicine, New York University Medical Center, New York, NY, 10016
Proc Am Assoc Cancer Res; 23:251 1982

Bis(chloromethyl)ether (BCME) and HCHO (formaldehyde) are carcinogens for the respiratory tissues of rats. BCME can be formed from HCHO + HCl. We are studying the interactions of these agents with DNA by measuring DNA damage

with the S-1 nuclease assay. BCME produced dose-related DNA damage up to 320 uM, which was not affected by the presence of dideoxythymidine (10 ug/ml). This indicates that rapid repair of DNA breaks did not occur under these conditions. The max amount of damage was not altered at the increased dose of 640 uM. Exposure to BCME for 15, 30, and 45 min produced the same amount of damage at all doses. This is expected from the short half life of BCME aqueous solutions. Formaldehyde produced no DNA damage but appears to have prevented the alkaline unwinding of control DNA. This was observed at doses of 300-2560 uM. The DNA damage produced by 1 hr incubation with 8 uM 4-NQO (4-nitroquinoline-1-oxide) was decreased in the presence of HCHO. A dose-related decrease in 4-NQO-induced damage was observed from 300 uM HCHO. This effect of HCHO can be interpreted as a consequence of its known ability to produce crosslinks in DNA and protein, which would prevent alkaline unwinding of DNA. (no Refs)

18. DEFECTIVE REMOVAL OF DNA CROSS-LINKS IN A REPAIR-DEFICIENT MUTANT OF CHINESE HAMSTER CELLS.

Meyn RE, Jenkins SF, Thompson LH
Dept. Physics, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
Cancer Res; 42(8):3106-3110 1982

To further understand the relationships between DNA damage, DNA repair, and cellular end points such as survival and mutation, the repair capacity of a DNA repair-deficient mutant (strain UV-20) of Chinese hamster ovary cells was characterized in response to DNA cross-linking agents. This mutant, previously shown to be hypersensitive to killing by both ultraviolet light and the cross-linking agent mitomycin C, was also found to be extremely sensitive to cis-diamminedichloroplatinum, another DNA cross-linking agent. The efficiency of DNA cross-link removal after treatment with mitomycin C or cis-diamminedichloroplatinum was measured using the technique of alkaline elution and compared in wild-type Chinese hamster ovary cells and strain UV-20. Wild-type cells removed 80 or 95% of the cross-links within 24 hr after treatment with cis-diamminedichloroplatinum or mitomycin C, respectively. In contrast, UV-20 cells, which were equally as susceptible to cross-link damage as were wild-type cells, removed only a small proportion of the cross-links made by either agent. These results emphasize the importance of DNA repair processes in modulating the cytotoxic effects of chemicals that produce DNA cross-link damage and suggest that cross-link repair in chinese hamster ovary cells is controlled by pathway that also repairs damage from ultraviolet radiation. (Author abstract) (26 Refs)

19. RECOVERY FROM POST-IRRADIATION INHIBITION OF DNA SYNTHESIS IN AN ULTRAVIOLET-SENSITIVE MUTANT MOUSE CELL.

Hama-Inaba H, Hieda-Shiomi N, Shiomi T, Sato K
Genetics Div., Natl. Inst. Radiological Sciences, 9-1, Anagawa-4, Chiba 260, Japan
Mutat Res; 104(4/5):305-309 1982

Rates of DNA synthesis after irradiation were measured in mouse lymphoma L5178Y cells, UV-sensitive variant Q31, and the hybrid L51.Q1 cells, and affected recovery of UV-inhibited DNA synthesis was observed in mutant cells. Mutant Q31 cells were more sensitive to the lethal effects of UV than were the parental cells and the sensitivity of hybrid L15.Q1 cells was almost equal to that of L5178Y cells. Results indicated that the trait that confers UV sensitivity to Q31 cells is recessive. The effects of UV irradiation were examined in all three cell lines. The rates of DNA synthesis were inhibited in a dose-dependent manner and the degrees of inhibition were approx the same in the three cell lines indicating that UV irradiation inhibited the DNA synthesis at least for the first hr through a common process in mutant, parent, and hybrid cell lines. The change in the rates of DNA synthesis/viable cell was pursued with time of incubation after irradiation. Results obtained with L5178Y cells showed a slight change (105%) in the rate in the sham-irradiated control after incubation. The time course of the rates of DNA synthesis/viable cell was examined in mutant Q31 cells. The sham-irradiated control showed a slight decrease for the first hr, a recovery thereafter, and a constant rate (102%). Results showed that the rates of DNA synthesis in Q31 cells partially recovered after doses of 2.4 and 5 Joule/square meter (J/m2), but the recovery was completely absent after a dose of 10 J/m2. (9 Refs)

20. MEASUREMENTS OF M. LUTEUS ENDONUCLEASE-SENSITIVE LESIONS BY ALKALINE ELUTION.

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Mutat Res; 94(2):263-276 1982

Endo-sites were quantitatively measured with alkaline elution by first digesting the cell lysates on an inert polycarbonate filter with an extract from Micrococcus luteus and then analyzing by alkaline elution. Endo-sites were easily detected with fluences of UV-radiation of less than 0.1 Joule/square meter (J/m2). Removal of these lesions was observed in normal human fibroblasts after 0.2 and 0.4 J/m2; negligible repair was observed in excision-deficient XP cells after up to 24 hr of repair incubation. Sites were also detected after irradiation with the methylating agent N-methyl-N-nitro-N-nitroguanidine (MNNG). With post-treatment incubation, the sites induced by MNNG decreased in normal human fibroblasts, human carcinoma cells, and carcinoma cells of the mer- phenotype which are more sensitive to alkylating agent damage. (16 Refs)

21. APURINIC ENDONUCLEASE (APE) ACTIVITY IN NUCLEAR FRACTIONS FROM FETAL RAT LIVER AND BRAIN: INVERSE CORRELATION WITH SUSCEPTIBILITY TO TRANSPLACENTAL CARCINOGENESIS BY ALKYLATING AGENTS (MEETING ABSTRACT).

Chen B, Feng XW, Rice JM
National Cancer Institute, Frederick, MD, 21701
Proc Am Assoc Cancer Res; 23:48 1982

Fetal rat brain is known to be deficient in at least some pathways of DNA repair. To investigate the possible role of an important repair enzyme, APE, in susceptibility of fetal rat tissues to transplacental aklyalting agents, an assay was developed based on template activity of bacteriophage lambda-h80dlacps DNA for beta-galactosidase (beta G) synthesis in a coupled transcription-translation system. Purified DNA was made apurinic (AP DNA) with acetic acid, neutralized and assayed for beta G template activity after preincubation with nuclear fraction or 100,000 g supernatant (S 100) from homogenized tissues from 17-20 day fetal Sprague Dawley rat brain or liver. AP DNA alone yielded 80% of control DNA activity. Pre-incubation of AP DNA with liver nuclear fraction decreased beta-G template activity to 50-70% of the AP DNA control (3 experiments). Neither nuclear nor S 100 fractions from either organ inhibited beta-G template activity of control DNA when added

to the beta-G synthesis system or when preincubated with control DNA prior to assay. Alkaline sucrose gradients revealed that AP DNA was reduced in size after incubation with liver nuclear fraction. The inhibitory activity in liver nuclear fraction thus has properties of an endonuclease specific for AP DNA. The lack of APE activity in fetal rat brain correlates with, and may contribute to DNA repair deficiency and high susceptibility to toxic and carcinogenic effects of alkylating agents. (no Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN INVERTEBRATES AND LOWER EUKARYOTES

22. REPAIR AND MUTAGENESIS OF PLASMID DNA MODIFIED BY ULTRAVIOLET IRRADIATION OR N-ACETOXY-N-2-ACETYLAMINOFLUORENE.

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Proc Natl Acad Sci USA; 79(13):4133-4137 1982

Plasmid DNA was modified in vitro to various extents with N-acetoxy-N-2-acetylaminofluorene or UV irradiation. The modified plasmid DNAs were then used to transform Escherichia coli strains having different repair capabilities. Both survival and mutagenesis frequencies of the plasmid were measured as a function of the number of lesions per plasmid molecule. The majority of N-2-acetylaminofluorene (AAF) adducts, like thymine dimers, were repaired by the excision (uvrA+-dependent) pathway. In rec+ strains, dose-dependent mutagenesis occurred in either AAF- or UV-modified plasmid DNA. This is in contrast with results obtained in recA- strains, in which only AAF adducts gave rise to a lower, but dose-dependent, mutagenesis frequency. In these recA- strains there was no UV mutagenesis. Unlike what is observed with phages, induction of the 'SOS' functions by UV irradiation of the bacteria prior to transformation did not increase the survival or the mutagenesis of the plasmid. (Author abstract) (47 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN BACTERIA

23. THE MUTAGENIC EFFECT OF DEOXYNUCLEOTIDE SUBSTRATE IMBALANCES DURING DNA SYNTHESIS WITH MAMMALIAN DNA POLYMERASES.

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Mutat Res; 94(2):413-419 1982

Relation between relative concentrations of incorrect and correct substrates and frequency of mutagenesis by mammalian DNA polymerases was studied in PhiX174 amber mutants. The mutation frequency and the two different loci on a biologically active DNA template was significantly affected by the ratio of incorrect to correct nucleotides during in vitro polymerization catalyzed by either DNA polymerase-alpha or DNA polymerase-beta. The results provide support for the hypothesis that altered nucleotide pools cause mutations in mammalian cells by decreasing the fidelity of DNA synthesis. (22 Refs)

24. SITE-DIRECTED INCORPORATION OF A CHEMICALLY SYNTHESIZED OLIGONUCLEOTIDE CONTAINING A CARCINOGEN-MODIFIED BASE, O6-METHYLGUANINE, INTO A BACTERIAL PLASMID GENOME (MEETING ABSTRACT).

Green CL, Essigmann JM
Massachusetts Institute of Technology, Cambridge, MA, 02139
Proc Am Assoc Cancer Res; 23:240 1982

Chemical carcinogen-DNA component adducts are believed to pose mutagenic risks to the genetic integrity of cells. In order to determine the possible mutagenic consequences of DNA synthesis past a DNA adduct, an oligonucleotide was chemically synthesized containing O(6)-methylguanine; this adduct is thought to induce GC to AT transitions during DNA replication. The chemically synthesized tetranucleotide (5'-dT(O6Me)GCA-3') was phosphorylated at its 5' terminus to a high specific activity by the action of T4 polynucleotide kinase in the presence of [gamma32-P]ATP. A bacterial plasmid vector was prepared to receive this chemically modified tetranucleotide. In parallel reactions, pBR322 was digested with PvuII and PstI, restriction endonucleases that each cut this DNA once. The overlapping 3' ends (5'-TGCA-3') of the PstI-treated genomes were excised with T4 polymerase. This DNA, blunt-ended at the PstI site, was mixed with PvuII-cut linear molecules. The mixture was denatured and allowed to reanneal to form heteroduplex circular molecules containing a 4-base gap in one of the DNA strands at the PstI recognition site. The phosphorylated, chemically adducted tetranucleotide was covalently integrated into this 4-base gap by DNA ligase. This DNA will be used to study fidelity of replication past, and repair of, this putative premutagenic lesion. (no Refs)

MACROMOLECULAR BINDING OF CARCINOGENS

25. DNA-BINDING PROTEIN FROM HELA CELLS THAT BINDS PREFERENTIALLY TO SUPERCOILED DNA DAMAGED BY ULTRAVIOLET LIGHT OR N-ACETOXY-N-ACETYL-2-AMINOFLUORENE.

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Biochim Biophys Acta; 697(2):202-212 1982

A DNA-binding protein was partially purified from extracts of HeLa cells by high-speed centrifugation and chromatography on DEAE-cellulose, phosphocellulose and ultraviolet light-irradiated DNA-cellulose columns. It eluted from the phosphocellulose column with 0.375 M potassium phosphate and from the ultraviolet light-irradiated DNA-cellulose column between 0.5 M and 1 M NaCl. The protein binds preferentially to supercoiled PM2 DNA treated with ultraviolet light or N-acetoxy-N-acetyl-2-aminofluorine, as compared to native supercoiled PM2 DNA. The binding is non-cooperative. Nicked or linear forms of PM2 DNA (damaged or untreated) are not efficient substrates, indicating a requirement of DNA supercoiling for DNA binding. The sedimentation coefficient of the protein estimated by glycerol gradient centrifugation is 2.0-2.5 S, corresponding to a molecular weight of about 20,000-25,000 if the protein is spherical. The binding to DNA irradiated with ultraviolet light or treated with acetoxyacetylaminofluorene is opti-

mal at around 100-200 mM NaCl and is relatively independent of temperature and pH. MgCl2 and MnCl2 at concentrations between 1 and 5 mM do not markedly affect the binding, but it is inhibited by sucrose, ATP and caffeine. The biological significance of the DNA-binding protein remains to be determined. It does not possess significant glycosylase, endonuclease or exonuclease activities. The dissociation equilibrium constant for the binding reaction of the protein to the ultraviolet light or acetoxyacetylaminofluorene-induced binding sites on DNA is estimated to be 4 x 10(-11) M. There are at least 1 x 10(5) DNA-binding protein molecules/HeLa cell. (Author abstract) (32 Refs)

26. N-2-ACETYLAMINOFLUORENE MODIFICATION OF POLY(DG-M5DC).POLY(DG-M5DC) INDUCES THE Z-DNA CONFORMATION.

Santella RM, Grunberger D, Nordheim A, Rich A
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Biochem Biophys Res Commun; 106(4):1226-1232 1982

Carcinogen induced conformational chages and the effect of N-2-acetylaminofluorene (N-Aco-AAF) modification on poly(dG-m5dC).poly(dG-m5dC) were investigated. The circular dichroism spectra of poly(dG-m5dC).poly(dG--m5dC) with various levels of acetylaminofluorene (AAF) modification are presented. With increasing levels of AAF, a decrease in the positive band at 280 nanometer (nm) and an increase in the negative band at 255 nm was observed. A sample with 3.5% modification underwent the B to Z transition with increasing Mg++ concentrations. A DNA sample modified with [14C] labeled AAF to an extent of 8.5% showed approx 50% digestion with S1 nuclease after 3 hr. In contrast, a 17.5% AAF modified sample of poly(dG-m5dC).poly(dG-m5dC) showed only 14% digestion after 3-hr incubation with S1 nuclease. The equilibrium binding level of the various polymers as a function of the concentration of N-Aco-AAF was determined. At the lowest concentration of N-Aco-AAF added, the methylated polymer was modified to a level of 6% compared to 3% with the unmethylated polymer. At higher concentrations of N-Aco-AAF, the level of AAF binding in the methylated polymer rose more rapidly than in the unmethylated polymer. Thus, the order of reactivity with AAF is poly(dG-m5dC).poly(dG-m5dC) greater than poly(dG-dC).poly(dG-dC) greater than poly(dG).poly(dC). Results indicated that the alternating polymer poly(dG-m5dC).poly(dG-m5dC) undergoes the B to Z transition at lower levels of AAF modification (10%) than required to convert the non methylated polymer (greater than 20%). (18 Refs)

27. EFFECT OF CHROMATIN DNASE ON DNA MODIFIED BY THE CARCINOGEN N-ACETOXY-2-ACETYLAMINOFLUORENE.

Vinter VG, Zotkina NL, Khamidullina NG
V. I. Ul'ianov-Lenin State Univ., Kazan, USSR
Eksp Onkol; 4(3):57-59 1982

To evaluate the role of the excision system in liver carcinogenesis, DNA treated with N-acetoxy-2-acetylaminofluorene (AAAF) was incubated with neutral chromatin DNAse. Comparison of the products of hydrolysis of native, AAAF-modified, and denatured DNA showed that the effect of DNAse on the modified DNA was similar to that on the denatured DNA. These findings indicated that neutral chromatin DNAse can recognize and excise the modified bases in native DNA. (15 Refs) (In RUS)

28. ORGANOTROPIC DIFFERENCES IN METABOLISM AND DNA BINDING OF 7,12-DIMETHYLBENZ(A)ANTHRACENE IN HUMAN FETAL CELLS (MEETING ABSTRACT).

Oravec CT, D'Ambrosio SM
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In Vitro; 18(3,part2):288 1982

DMBA (7,12-Dimethylbenz(a)anthracene) is a potent polycyclic aromatic hydrocarbon carcinogen, both transplacentally and in the adult, when activated to an electrophilic form. The rate of metabolism and DNA binding capacity of DMBA was compared in vitro in cells derived from human fetal brain, dermis, kidney, liver, intestine and lung. Intestinal cells metabolized approximately 30%, while the other cells tested (brain, liver, dermal, lung and kidney) metabolized 2.5-10% of the DMBA during a 48 h period. Using HPLC (high performance liquid chromatography), qualitative as well as quantitative differences in the metabolite profiles were observed in each cell culture. The level of DMBA binding to cellular DNA was of the order: intestine greater than lung greater than liver greater than dermal greater than kidney. This order parallels the metabolic rate except that kidney was much lower than expected. These studies show that DNA binding and total metabolism is different in cells from different human fetal organs. (no Refs)

29. QUANTITATION OF AFLATOXIN B1-MODIFIED DNA USING MONOCLONAL ANTIBODIES.

Groopman JD, Haugen A, Goodrich GR, Wogan GN, Harris CC (c/o Harris) Lab. Human Carcinogenesis, NCI, Bethesda, MD, 20205
Cancer Res; 42(8):3120-3124 1982

Five monoclonal antibodies were obtained after fusion of mouse P3 x 63 myeloma cells with spleen cells isolated from BALB/c mice that had been immunized with aflatoxin B1-adducted DNA complexed with methylated bovine serum albumin. Selected hybridomas were found to produce monoclonal antibodies specific for modified DNA containing both the 2,3-dihydro-2-(N7-guanyl)-3-hydroxyaflatoxin B1 and the putative 2,3-dihydro-2-(N5-formyl-2',5', 6'-triamino-4'-oxo-N5-pyrimidyl)-3-hydroxyaflatoxin B1, suggesting that these DNA adducts share a common antigenic determinant. Enzyme immunoassay conditions using the monoclonal antibodies were optimized, and DNA isolated from the livers of rats given dosages of aflatoxin B1 ranging from 0.01 to 1.0 mg aflatoxin B1 per kg body wt was tested. A level of modification in DNA of 1 aflatoxin B1 residue per 1,355,000 nucleotides can be quantitatively measured. Monoclonal antibodies will be useful probes for studying the molecular interactions of aflatoxin B1 with DNA and the occurrence of aflatoxin B1:DNA adducts in tissues and cells of humans exposed to this environmental carcinogen. (Author abstract) (26 Refs)

30. FORMATION OF 6-DIMETHYLCARBAMYLOXY-DGUO, 6-DIMETHYLAMINO-DGUO AND 4-DIMETHYLAMINO-DTHD FOLLOWING IN VITRO REACTION OF DIMETHYLCARBAMYL CHLORIDE WITH CALF THYMUS DNA AND 6-DIETHYLCARBAMYLOXY-DGUO FOLLOWING IN VITRO REACTION OF DIETHYLCARBAMYL CHLORIDE WITH CALF THYMUS DNA.

Segal A, Solomon JJ, Mate U, Van Duuren BL
Lab. Organic Chemistry and Carcinogenesis, Inst. Environmental Medicine, New York Univ. Sch. Medicine, New York, NY, 10016
Chem Biol Interact; 40(2):209-231 1982

The rodent carcinogens dimethylcarbamyl chloride (DMCC) and diethylcarbamyl chloride (DECC) react with dGuo (pH 7.0-7.5, 37 C, 4 hr) to form the O6-acyl derivatives 6-dimethylcarbamyloxy-2'-deoxyguanosine (6-DMC-dGuo) and 6-diethylcarbamyloxy-2'-deoxyguanosine (6-DEC-dGuo), respectively. Reaction of DMCC with dThd under identical conditions yielded 4-dimethylamino-thymidine (4-DMA-dThd). Compounds 6-DMC-dGuo and 6-DEC-dGuo undergo a nucleophilic aromatic substitution reaction with dimethylamine (DMA) to form 6-dimethylamino-2'-deoxyguanosine (6-DMA-dGuo) via displacement of the C-6 dialkylcarbamyloxy moiety. The substitution reaction did not take place when diethylamine or NH3 were substituted for DMA. The structures of the new compounds 6-DMC-dGuo, 6-DEC-dGuo, 4-DMA-dThd and 6-DMA-dGuo were deduced from chemical analyses and syntheses, UV and nuclear magnetic resonance (NMR) spectra and electron impact, isobutane chemical ionization and source insertion isobutane chemical ionization mass spectra. It was postulated that 4-DMA-dThd was formed following reaction of the transient intermediate 4-DMC-dThd with DMA formed by hydrolysis of DMCC. Calf thymus DNA was reacted in vitro with DMCC (pH 7.0-7.5, 37 C, 4 hr) and the modified DNA hydrolyzed enzymatically to 2'-deoxynucleosides. Compounds 6-DMC-dGuo, 4-DMA-dThd and 6-DMA-dGuo were identified in the hydrolysate by high-pressure liquid chromatography (HPLC). In an identical manner 6-DEC-dGuo was identified following in vitro reaction of DECC with calf thymus DNA. Compounds 6-DEC-dGuo and 6-DMC-dGuo possess novel structures with respect to the types of adducts known to be formed between carcinogens and bases in DNA. The implications of these findings with respect to chemical mutagenesis and carcinogenesis is discussed. The structural relationship between N4-dimethyl-5-methylcytosine (4-dimethylamino-Thy) formed in DNA following in vitro reaction with DMCC and 5-methylcytosine, the only modified base found in vertebrate DNA is noted. (Author abstract) (47 Refs)

31. FORMATION AND BIOLOGICAL PROPERTIES OF DNA ADDUCTS FROM THE HEPATOCARCINOGEN, N-METHYL-4-AMINOAZOBENZENE (MEETING ABSTRACT).

Tullis DL, Baetcke KP, Kadlubar FF
National Center for Toxicological Research, Jefferson, AR, 72079
Proc Am Assoc Cancer Res; 23:241 1982

In previous studies, 3 major in vivo DNA adducts of the hepatocarcinogenic aminoazo dye, N-methyl-4-aminoazobenzene (MAB), were identified. These were 3-(deoxyguanosin-N(2)-yl)-MAB (N(2)-dG), N-(deoxyguanosin-8-yl)-MAB (C8-dG), and 3-(deoxyadenosin-N(2)-yl)-MAB (N(6)-dA). To investigate the role of these adducts in tumor induction, male S/D rats were fed diets containing 0.06% [3',5'-3H]MAB (100 mCi/mmol) for 1, 3, or 5 weeks and then sacrificed at 0, 1, or 3 days after the end of the treatment period. DNA was isolated from carcinogen target (liver) and non-target (kidney and spleen) tissues, and was enzymatically hydrolyzed to nucleosides. Immediately after each treatment period, the total level of carcinogen binding to DNA was 3 to 10-fold higher in target than in non-target tissues. However, the total level of binding in the liver rapidly decreased to one-half of the original level at 3 days post-treatment. When the individual adducts from target and non-target tissues were compared at the end of each treatment period, the highest observed levels of each adduct were found in the liver. The N(2)-dG adduct was always predominant, followed by C8-dG, N(6)-dA, and an unidentified adduct. By 3 days after MAB dosing, the hepatic levels of C8-dG and the unidentified adduct had decreased 50-90% to levels similar to those found in kidney and spleen. Hepatic N(6)-dA, which in previous studies appeared to be persistent after acute doses, decreased 70-80% at 3 days after chronic treatment. In contrast, hepatic N(2)-dG remained at a high level and accounted for 10-15 adducts/10(6) nucleotides after 5 weeks of dosing. (no Refs)

32. METABOLIC PATHWAYS FOR THE CARCINOGEN, BENZIDINE, WHICH RESULT IN COVALENT BINDING TO DNA (MEETING ABSTRACT).

Frederick CB, Martin CN, Weis CC, Kadlubar FF
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Proc Am Assoc Cancer Res; 23:322 1982

Benzidine (BZ), a urinary bladder carcinogen in humans and dogs, induces hepatic tumors in mice and rats. In recent studies, we identified a single carcinogen-DNA adduct, N-(deoxyguanosin-8-yl)-N'-acetyl-BZ, in mouse and rat liver following an ip dose of BZ or N-acetylbenzidine (N-ABZ). N,N'-Diacetylbenzidine (DABZ) did not produce a detectable level of DNA binding. To determine which metabolic activation pathways result in DNA binding in vivo, we examined the N-acetylation, N-hydroxylation, N-deacetylation, and O-esterfication of BZ and its derivatives in vitro using rat liver subcellular fractions. N-ABZ, a known metabolite of BZ, was preferentially oxidized on the amide nitrogen by NADPH-fortified microsomes to yield N-hydroxy-N-ABZ. N'-Hydroxy-N-ABZ was not detected. N-Hydroxy-N-ABZ was then N-acetylated by liver cytosol and acetyl CoA to give N-hydroxy-DABZ. N-Hydroxy-DABZ was further selectively deacetylated by hepatic microsomes to yield N'-hydroxy-N-ABZ. Both of these were substrates for purified hepatic N,O-acyl-transferase, resulting in intra- and intermolecular acyl transfer, respectively, and subsequent covalent binding to added DNA. Enzymatic hydrolysis of the DNA and high pressure liquid chromatography yielded the identical C-8-deoxy-guanosine adduct found in vivo. Similar results, albeit at lower levels of binding, were obtained by reaction of N'-hydroxy-N-ABZ directly with DNA. Thus, these data suggest that N'-hydroxy-N-ABZ and N-hydroxy-DABZ are proximate carcinogenic metabolites of BZ in the rat. (no Refs)

33. THE PRESENCE OF CARRIER FOR ACTIVATED BENZO[A]PYRENE METABOLITE IN HUMAN AND MOUSE CELLS (MEETING ABSTRACT).

Lo KY, Kakunaga T, Yamamoto S
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Proc Am Assoc Cancer Res; 23:245 1982

It has long been an unsolved question how the ultimate form of benzo[a]pyrene, (+/-)7 beta,8 alpha-dihydroxy-9 alpha,10 alpha-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene (BPDEI)

reaches nuclear DNA in spite of its instability in aqueous solution. The object of this study is to determine the fate of BPDEI in cells, and clarify its biological implication. In normal diploid human fibroblasts and mouse A31-1-1 cells treated with BPDEI (0.33-3.3uM), the removal of BPDEI-DNA adducts showed a biphasic kinetics-a rapid removal phase followed by a slow removal phase. Removal of BPDEI adducts in the repair-deficient Xeroderma pigmentosum cells (XP12BE and 1261) under the same conditions gave biphasic kinetics also--a fast removal phase followed by a plateau phase. These findings suggest the possibility that the rapid removal of DNA adducts in the first phase reflects the decline of amounts of BPDEI which remains chemically active in cells for a few hours, and interact with DNA upon cell lysis. Plasmid PBR322 DNA was added to the lysates of the BPEDI-treated cells, and BPDEI bound to plasmid DNA was measured. The amount of BPDEI-DNA adduct formed in the plasmid DNA decreased, in parallel with those in host DNA, with time of post-incubation. The cell components which stabilize or carry BPDEI were searched in fractionated cell lysates by using this method. It was found that microsomal fraction had the ability to transfer BPDEI to DNA, however, partially purified P450 could not. (no Refs)

34. COMPARISON OF LEVELS OF BENZO(A)PYRENE-7,8-DIOL-9,10-EPOXIDE (BPDE) DIASTEREOMERS AND ENANTIOMERS COVALENTLY BOUND IN VIVO TO MACROMOLECULAR COMPONENTS OF WHOLE EPIDERMIS VERSUS THE BASAL CELL LAYER (MEETING ABSTRACT).

Pelling JC, Slaga TJ
Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN, 37830
Proc Am Assoc Cancer Res; 23:246 1982

The binding of anti-BPDE, the ultimate carcinogenic metabolite of benzo(a)pyrene, and its non-carcinogenic syn-diastereomer was investigated in mouse epidermis in vivo. Sencar mice were exposed for various times to topically applied (+)anti and (+)syn diastereomers of BPDE and the levels of BPDE bound to cell macromolecules were determined. A comparison of the amounts of (+)anti and (+)syn-BPDE bound to RNA, DNA, and protein isolated from whole epidermis indicated that a differential binding pattern had occurred, with 2x more (+)anti-than (+)syn-BPDE present in DNA after 24 hours. In contrast, no significant difference in levels of (+)anti and (+)syn adducts was observed in macromolecules isolated from purified basal cells, the presumed target cell population for initiation. Additional binding studies with the optically pure (+) and (-) enantiomers of BPDE-anti indicated a significant difference in levels of adducts formed, with 2-3x more (+) anti- than (-) anti-BPDE bound to DNA purified from the basal cell layer. The higher level of binding by (+)anti-BPDE to DNA of basal cells reflects the previously demonstrated relative tumorigenic activities of these two enantiomers. (no Refs)

35. XANTHINE OXIDASE-CATALYZED REDUCTION OF 1-NITROPYRENE TO A POTENTIALLY MUTAGENIC DNA-BINDING SPECIES (MEETING ABSTRACT).

Howard PC, Beland FA, Evans FE, Heflich RH
The National Center for Toxicological Research, Jefferson, AR, 72079
Proc Am Assoc Cancer Res; 23:242 1982

Since metabolic reduction of this nitroarene would be expected to yield a reactive N-hydroxy derivative, we have examined the ability of a mammalian nitroreductase, xanthine oxidase, to catalyze the binding of nitropyrene to DNA. Incubation of 20 uM [4,5,9, 10-3H]1-nitropyrene (117 mCi/mmol), 3.7 mM hypoxanthine, 0.5 U/ml xanthine oxidase and 2 mg/ml calf thymus DNA gave a linear increase in DNA adduct formation over a 60 min period. Covalent binding was inhibited by allopurinol, a xanthine oxidase inhibitor, and by heat denaturation of the enzyme. Nitropyrene-DNA binding also occurred when hypoxanthine was replaced with xanthine, albeit at a lower level. Enzymatic hydrolysis of the DNA and subsequent analysis by high pressure liquid chromatography indicated the presence of one major nitropyrene-deoxyribonucleoside adduct. The product was characterized by electron impact in-beam desorption mass spectrometry and 500 MHz 1H-nuclear magnetic resonance spectroscopy as N-(deoxyguanosin-8-yl)-1-aminopyrene. When Salmonella typhimurium strain TA1538 was incubated with 3H-1-nitropyrene in suspension culture for 6 hr, a time-dependent linear increase in total macromolecular binding and reversion frequency was observed. Bacterial DNA was isolated by hydroxylapatite chromatography and enzymatically hydrolyzed to nucleosides, to yield one major adduct with a retention time identical to N-(deoxyguanosin-8-yl)-1-aminopyrene. (no Refs)

36. MODIFICATION OF DEOXYGUANOSINE VIA ALPHA-HYDROXYLATION OF N-NITROSOPYRROLIDINE (MEETING ABSTRACT).

Chung FL, Hecht S
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Proc Am Assoc Cancer Res; 23:249 1982

The structures of the DNA adducts formed from cyclic nitrosamines, such as N-nitrosopyrrolidine, have not been elucidated. We studied the reactions of alpha-acetoxy-N-nitrosopyrrolidine (alpha-OAcNPYR) and 4-(N-carbethoxy-N-nitrosamino)butanal (CNB) with deoxyguanosine, catalyzed by porcine liver esterase, in pH 7.0 buffer at 37 C. Under these conditions, alpha-OAcNPYR and CNB are both converted to the intermediate, 3-formylpropyldiazo-hydroxide, the potential ultimate carcinogen of NPYR resulting from metabolic alpha-hydroxylation. Two major deoxyribonucleoside products, A and B, were formed in the reaction of alpha-OAcNPYR or of CNB with deoxyguanosine. A and B were isolated by high performance liquid chromatography (HPLC) and their ultraviolet spectra, desorption chemical ionization mass spectra (M+1, m/e 338), electron impact mass spectra of their trimethylsilyl derivatives (M+, m/e 625), and nuclear magnetic resonance spectra determined. The spectral data indicate that A and B are N-1, N2 substituted tricyclic deoxyguanosine derivatives. Hydrolysis of A or B gave a product with identical HPLC retention volume as one obtained by incubation of NPYR, rat liver 9000 x g supernatant, and [14C]guanosine or [14C]guanosine monophosphate, followed by hydrolysis. The results of this study contrast to those obtained with acyclic nitrosamines, which give mainly 7-alkylation of guanosine and suggest that the mechanisms by which cyclic and acyclic nitrosamines damage DNA may be quite different. (no Refs)

37. HORSERADISH PEROXIDASE/HYDROGEN PEROXIDE (HRP/H2O(2)) BINDING OF POLYCYCLIC AROMATIC HYDROCARBONS (PAH) BY ONE-ELECTRON OXIDATION (MEETING ABSTRACT).

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Eppley Institute for Research in Cancer, University of Nebraska Medical Center, Omaha, NE, 68105
Proc Am Assoc Cancer Res; 23:239 1982

Several lines of evidence indicate that HRP/H2O2 catalyzes binding of PAH by one-electron oxidation. However, proof lies in elucidating adducts obtained between PAH and biologic macromolecules. The carcinogenic 6-methylbenzo[a]pyrene (BP-6-CH(3)), in which activation by one-electron oxidation occurs at the 6-methyl group, was accordingly used. Calf thymus DNA (1 mg/ml), HRP (Type II, 0.1 mg/ml), 5 X 10-4M H2O2 and 70 uM [14C]BP-6-CH3 were incubated in 0.067 M Sorenson buffer, pH 7, for 1 hr at 37 C. After purification DNA (1 mg/ml) in 0.05 M Bis-Tris, 5 mM MgCl2, pH 7.1 was incubated with 0.1 mg/ml deoxyribonuclease I for 3 hr at 37 C under argon. The mixture, partially saturated with (NH(4))2SO4, was extracted 3 times with n-butanol. The residue, after evaporation of n-butanol, was analyzed by reverse-phase high performance liquid chromatography and its profile was compared to that from the hydrolyzed BP-6-CH2BR and DNA. Only a major adduct was present in the HRP/H2O(2)-activated system and the same adduct was also in the BP-6-CH2BR-DNA system. Both collected adducts co-chromatographed in 3 additional elution systems with the adduct obtained from deoxyguanosine (dG) and BP-6-CH2Br. Nuclear magnetic resonance spectra of the synthetic adduct showed that BP-6-CH3 binds through the methyl group to the 2-amino group of dG. Thus, structure elucidation of the HRP-H2O(2)-catalyzed adduct between BP-6-CH3 radical cation is the reactive intermediate responsible for the binding and HRP/H2O2 activation occurs by one-electron oxidation. (1 Ref)

38. FORMATION OF A 7-HYDROXYMETHYL-12-METHYLBENZ[A]ANTHRACENE-DNA ADDUCT FROM DMBA IN MOUSE EPIDERMIS (MEETING ABSTRACT).

DiGiovanni J
The Wistar Institute, Philadelphia, PA, 19104
Proc Am Assoc Cancer Res; 23:244 1982

The present study was designed to investigate the role of 7-hydroxymethyl-12-methylbenz[a]anthracene (7-OHM-12-MBA) in the covalent binding of DMBA (dimethylbenzanthracene) to mouse epidermal DNA. The covalent binding of [3H]7-OHM-12-MBA to mouse epidermal DNA was compared with [3H]DMBA. Twenty-four hours after application of [3H]7-OHM-12-MBA (400 nmol) or [3H]DMBA (10 nmol) to the skins of SENCAR mice, the covalent binding was 29.0 or 4.5 pmol/mg epidermal DNA, respectively. The isolated DNA samples were hydrolyzed to deoxyribonucleosides and chromatographed on Sephadex LH20 columns. With DMBA, four distinct DMBA-DNA adduct peaks eluted after the p-(nitrobenzyl)-pyridine (p-NBP) marker. A fifth, early eluting peak, cochromatographed with p-NBP marker. When [3H]7-OHM-12-MBA was applied to the skins of mice, three distinct DNA-adduct peaks were observed. The major 7-OHM-12-MBA-DNA adduct eluted with the p-NBP marker and cochromatographed on high performance liquid chromatography with the early eluting DMBA-DNA adduct. The other 7-OHM-12-MBA-DNA adducts did not cochromatograph with any DMBA-DNA adducts. Interestingly, benzo[e]pyrene, which markedly inhibited DMBA tumor-initiation and DNA-adduct formation in SENCAR mice, had no effect on DNA-adduct formation with 7-OHM-12-MBA. The results suggest that a hydroxymethyl-metabolite gives rise to a minor DMBA-DNA adduct in mouse skin and that 7-OHM-12-MBA, when applied topically, may be processed by epidermal cells in a manner different from that of DMBA. (2 Refs)

39. EVIDENCE FOR MICROSOME-MEDIATED COVALENT BINDING OF DIETHYLSTILBESTROL TO DNA OR NUCLEOTIDES (MEETING ABSTRACT).

Liehr JG, DaGue BB
University of Texas Health Science Center, Houston, TX, 77025
Proc Am Assoc Cancer Res; 23:916 1982

In order to examine the possible role of estrogenic hormones as initiators of carcinogenesis, binding of the synthetic estrogen diethylstilbestrol (DES) to deoxynucleosides and calf thymus DNA was studied in an in vitro microsome-mediated reaction system. Binding levels were influenced by the reaction time, source of microsomes, and concentrations of DES, DNA, and microsomal cyt P450 (or P448) used in the reaction system. Reactions of 14C-DES (56 mCi/mmole) with 0.36 mM calf thymus DNA (heat denatured) or 3.3 mM dGMP catalyzed by phenobarbital-induced rat liver microsomes for 2.5 hrs produced 1300 and 50 adducts/ 10(6) nucleotides x nmole cyt P450), respectively. Binding of DES to DNA and dGMP in the presence of boiled microsomes was 1% and 10%, respective, of that found in active microsome catalyzed reactions. Evidence for the covalent nature of DES binding to DNA and deoxynucleotides was obtained from the persistence of bound radioactivity after exhaustive extraction of reactions with organic solvents and, in the case of DNA, multiple precipitations from ethanol. Furthermore, it has been possible to separate by reverse phase high pressure liquid chromatography unreacted deoxynucleosides and the radioactive DES-deoxynucleosides obtained from organic solvent-extracted and alkaline phosphatase-treated binding reactions of 14C-DES and deoxynucleotides. (no Refs)

EFFECT OF CARCINOGENS ON MACROMOLECULAR SYNTHESES

40. INCREASED AMOUNTS OF DOUBLE-STRANDED RNA IN THE CYTOPLASM OF RAT LIVER FOLLOWING TREATMENT WITH CARCINOGENS.

Ciawson GA, Smuckler EA
(c/o Smuckler) Dept. Pathology, HSW547, Univ. California, San Francisco, CA, 94143
Cancer Res; 42(8):3228-3231 1982

Cytoplasmic RNA was isolated from control rats or at 48 hr following carcinogen administration. A significant quantity (0.6%) of double-stranded RNA was present in control preparations, as assessed by digestion with RNase III. Following carcinogen treatment of rats, this percentage increased significantly. The results suggest that the altered transport of repetitive sequences which is induced by carcinogen treatment involves alterations in the metabolism of double-stranded RNA sequences. (Author abstract) (60 Refs)

REVIEWS

41. GENE AMPLIFICATION.

Schimke RT
Dept. Biological Sciences, Stanford Univ., Stanford, CA
Gene Amplification. Cold Spring Harbor, NY, Cold Spring Harbor Laboratory, 339 pp., 1982.

Gene duplication and amplification studies are reviewed and extended abstracts of a conference on gene amplification are presented. Examples of gene amplification include dihydrofolate reductase gene amplification in murine and Chinese hamster ovary cell lines; in a methotrexate-resistant human leukemia cell line (K562); in rat hepatoma cells; in antifolate-sensitive and -resistant Chinese hamster lung cells; in antifolate-resistant, vincristine-resistant, and human neuroblastoma cells; in reciprocally cross-resistant uptake mutants of neuroblastoma; and in vincristine-resistant Chinese hamster ovary cells. Phenotypic reversion as a consequence of gene amplification, altered regulation of the mouse metallothionein-I gene, amplification of the gene for asparagine synthetase, and control of DHFR DNA replication and messenger RNA production. Other aspects of gene amplification are discussed, including studies involving the SEWA mouse tumor, clonogenic human tumor cells, human small cell lung cancer, Drosophila, and chicken actin genes during myogenesis. Molecular structures of amplified DNA structures in mouse cell lines and Chinese hamster ovary cells are described and methods for cloning amplified DNA, analysis of CAD gene amplification, and cloning and analysis of double minute DNA are reviewed. Mechanisms of gene amplification are proposed. Chromosomal alterations are discussed with respect to nonrandom gain of chromosomes in human malignant hematologic diseases, a chromosome defect in most cancers, the biologic role for chromatid exchange in mammalian somatic cells, and a common denominator in the tumorigenic action of viral oncogenes and nonrandom chromosomal changes. (295 Refs)

42. MECHANISMS FOR CHROMOSOMAL ABERRATIONS IN MAMMALIAN CELLS.

Natarajan AT, Zwanenburg TS
Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Wassenaarseweg 72, 2333 AL Leiden, The Netherlands
Mutat Res; 95(1):1-6 1982

Lesions responsible for chromosomal aberrations (CA) induced by ionizing radiations, role of base damage in x-ray-induced CA, and experiments involving repair inhibitors are discussed. The frequencies of DNA-double strand breaks induced by x-rays alone, as well as in combination with Neurospora crassa endonuclease (NE) were measured by neutral sucrose-gradient centrifugation analysis to confirm the cytological findings and their interpretation. X-irradiation of CHO cells with 30 kilorad led to 8.8 double-strand breaks/10(10) dalton of DNA, and post treatment of the cells with NE led to a doubling of the frequencies of double-strand breaks induced by x-rays supporting the conclusion that DNA double-strand breaks are the most probable lesions that lead to the formation of CA induced by ionizing radiations. When G0 or G1 cells from patients with ataxia telangiectasia were irradiated with x-rays, both chromosome and chromatid types of aberration were obtained in contrast to mainly chromosome-type aberrations obtained in normal cells. Several inhibitors of DNA synthesis, such as cytosine arabinoside, aphidicolin, and hydroxyurea, as well as inhibitors of poly(ADP-ribose) polymerase (PRP), have been used in x-ray experiments involving human peripheral blood lymphocytes. When human peripheral blood lymphocytes were irradiated and post treated with inhibitors of PRP, such as 3-aminobenzamide, for at least 6 hr prior to stimulation, a doubling of the frequency of aberrations was observed. The results supported the conclusion that DNA double-strand breaks are the most important lesions responsible for radiation-induced CA. (19 Refs)

43. DNA REPAIR ASSAYS AS TESTS FOR ENVIRONMENTAL MUTAGENS. A REPORT OF THE U.S. EPA GENE-TOX PROGRAM.

Larsen KH, Brash D, Cleaver JE, Hart RW, Maher VM, Painter RB, Sega GA
Environmental Mutagen Information Center, Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 99(3):287-318 1982

Repair replication (RR) assayed in isopycnic gradients, RR measured by benzoylated naphthoylated diethylaminoethyl (BND) cellulose, RR assayed by bromodeoxyuridine (BUdR) photolysis, alkaline elution assays, repair of single-strand breaks measured in alkaline sucrose gradients, and loss of adducts from DNA are reviewed. BND cellulose chromatography has not been widely adopted for measurement of RR, despite its relative ease and the fact that multiple samples can be processed simultaneously. The BUdR photolysis method is better suited for screening than most of the other DNA repair assays; it can be well controlled using internal standards, and, if standard repair intervals are used, produces data suitable for precise quantitative comparisons. Alkaline elution appears to be useful for identification of DNA-damaging agents if appropriate quantification is performed; it is sensitive, easy to perform and analyze, applicable both in vivo and in vitro studies, and could be used for simultaneous processing of multiple samples. The alkaline sucrose gradient technique for determining DNA repair appears to have limited usefulness for hazard evaluation. The chemicals tested in the various DNA repair assays are listed in the summary table with chemical classifications, and, where available, carcinogenicity assessments. Most of the chemicals used were known inducers of DNA damage and repair, and known mutagens and carcinogens. Of the 49 compounds listed, 23 are alkylating agents, and an additional 11 are polycyclic aromatic hydrocarbons. On theoretical grounds, evidence of DNA repair is a poor indicator of genetic risk. Thus, risk assessment based on repair data must be highly speculative. (130 Refs)

44. RELATIONSHIP OF DNA TERTIARY AND QUATERNARY STRUCTURE TO CARCINOGENIC PROCESSES.

Lipetz PD, Galsky AG, Stephens RE
Dept. Radiology, Ohio State Univ., Columbus, OH, 43210
Adv Cancer Res; 36:165-210 1982

DNA superstructure as studied in nucleoids (permeabilized and protein-depleted nuclei) and possible correlations between modification of the tertiary (supercoiling) and quaternary (supercoiled domains) levels of organization and carcinogenic processes are reviewed. Evidence that the nucleoid technique can be used to quantify extremely low levels of DNA strand breaks (less than 1/4.4 x 10(10) daltons of DNA) is discussed. Chromatin origins of DNA supercoiling; physiological relevance of decreased nucleoid DNA supercoiling; novobiocin and nalidixic acid as probes of DNA supercoiling; prokaryotic DNA supercoiling; and eukaryotic DNA superstructure are discussed. Crown gall tumorigenesis, chronic lymphocytic leukemia, 12-O-tetradecanoyl-phorbol-13-acetate-induced alter-

ations of DNA superstructure in normal human cells and chromatin damage and repair are addressed. The relationship of DNA superstructure to the processes of carcinogenesis, carcinogenic promotion, and Z DNA is discussed. DNA superstructure studies may lead to a resolution of the conflict between the idea that neoplastic transformation results from altered informational flow from DNA (as in somatic mutation) and the concept that membrane-associated events lead to malignant transformation. DNA superstructure could be responsive to both levels of control. (211 Refs)

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As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. ASBESTOS CARCINOGENESIS: ASBESTOS INTERACTIONS AND EPITHELIAL LESIONS IN CULTURED HUMAN TRACHEOBRONCHIAL TISSUES AND CELLS.
Hanges A, Harris C
Div. Cancer Cause and Prevention, NCI, Bethesda, MD
Recent Results Cancer Res; 82:32-42 1982

2. REVIEW: ORAL CONTRACEPTIVES AND MENOPAUSAL ESTROGENS IN RELATION TO BREAST NEOPLASIA.
Brzezinski A, Schenker JG
Dept. Obstetrics and Gynecology, Hadassah Univ. Hosp., POB 12000, 91120 Jerusalem, Israel
Isr J Med Sci; 18(4):433-438 1982

3. LIVER DISEASES DUE TO HORMONAL CONTRACEPTIVES.
Lie TS
Chirurgische Klinik und Poliklinik, Universitat, Sigmund-Freud-Str. 25, D-5300 Bonn 1, W. Germany
MMW; 124(20):489-494 1982
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4. THE WORK OF THE NRPB 1977/80 AND A REVIEW OF THE FIRST 10 YEARS.
National Radiological Protection Board
Natl. Radiological Prosection Board, Chilton, Didcot, Oxfordshire OX11 0RQ, England
The Work of the NRPB 1977/80 and a Review of the First 10 Years. Chilton, Didcot, Oxfordshire, National Radiological Protection Board, 70 pp., 1981.

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5. ALCOHOL AND CARCINOGENESIS.
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Schwerpunkt Gastroenterologie, Medizinische Universitatsklinik, Bergheimer Str. 58, D-6900 Heidelberg 1, W. Germany
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Beach RS, Gershwin ME, Hurley LS
Dept. Internal Medicine, Div. Rheumatology-Clinical Immunology, Univ. Calif., Davis, CA, 95616
Nutr Cancer; 3(3):172-191 1982

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7. TRENDS IN CANCER INCIDENCE: CAUSES AND PRACTICAL IMPLICATIONS. PROCEEDINGS OF A SYMPOSIUM HELD OSLO, NORWAY, 6-7 AUGUST 1980.
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The Cancer Registry Norway, Montebello, Oslo 3, Norway
Trends in Cancer Incidence: Causes and Practical Implications, Proceedings of a Symposium held Oslo, Norway, 6-7 August 1980. Washington, D. C., Hemisphere Publishing Corporation, 446 pp., 1982.

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Nuffield Dept. Clinical Medicine, Radcliffe Infirmary, Univ. Oxford, Oxford, England
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9. NASAL CARCINOMA IN WOODWORKERS: A REVIEW.
Wills JH
Sch. Medicine, Uniformed Services Univ. Health Sciences, 4301 Jones Bridge Road, Bethesda, MD, 20814
JOM; 24(7):526-530 1982

10. AIR POLLUTION AND CANCER. A REVIEW OF EXPERIMENTAL INVESTIGATIONS.
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(c/o Nielsen), Stigardsvej 2, DK-2900 Hellerup, Denmark
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Am J Epidemiol; 116(1):42-56 1982

12. INHALATION CARCINOGENESIS: AN OVERVIEW.
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Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
Adv Cancer Res; 36:149-163 1982

15. RELATIONSHIP OF DNA TERTIARY AND QUATERNARY STRUCTURE TO CARCINOGENIC PROCESSES.
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Adv Cancer Res; 36:165-210 1982

16. ROLE OF ENZYMATIC METHYLATION OF DNA IN CELL DIFFERENTIATION AND TRANSFORMATION.
Fedorov NA
Central Res. Inst. Hematology and Blood Transfusion, Moscow, USSR
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Socinski EM
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21. MOLECULAR EPIDEMIOLOGY AND CARCINOGEN-DNA ADDUCT DETECTION: NEW APPROACHES TO STUDIES OF HUMAN CANCER CAUSATION.
Perera FP, Weinstein IB
Div. Environmental Sciences, Columbia Univ., New York, NY, 10032
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Mutat Res; 98(3):377-387 1982

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Environmental Mutagen Information Center, Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 98(3):287-318 1982

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MECHANISMS OF CARCINOGENESIS

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DECEMBER, 1982

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BIOLOGICAL ASPECTS OF DNA ALTERATION AND REPAIR IN RELATION TO CARCINOGENICITY

1. NEOPLASTIC TRANSFORMATION OF HUMAN CELLS IN CULTURE ASSOCIATED WITH DEFICIENT REPAIR OF LIGHT-INDUCED CHROMOSOMAL DNA DAMAGE.

Parshad R, Sanford KK, Jones GM, Tarone RE
(c/o Sanford) Lab. Cellular and Molecular Biology, NCI, Building 37, Room 2DO2, Bethesda, MD, 20205
Int J Cancer; 30(2):153-159 1982

Two lines of normal human skin fibroblasts and five derivative lines transformed in culture to neoplastic cells by chemical carcinogens were compared with respect to chromatid breakage produced by exposure to low-intensity fluorescent light (cool-white, 4.6 W/m2) during pre-S, S, and late S-G2 periods of the cell cycle. Five additional normal human cell lines and a line derived from a lung adenocarcinoma were also examined for chromatid damage following light exposure during pre-S and late S-G2. The frequency of chromatid breaks induced by pre-S light exposure in the neoplastic cells is not significantly different from that in the normal cells. However, addition of

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caffeine, an inhibitor of DNA repair, to the culture medium following light exposure significantly increases the frequency of chromatid breaks in the neoplastic but not in the normal cells. One possible explanation for these observations is that the normal cells, known to have effective excision repair, remove the DNA damage, whereas the neoplastic cells, presumably deficient in excision repair, handle the damage during S by a caffeine-sensitive mechanism. Furthermore, the neoplastic but not the normal cells, show significant increases in chromatid breaks when exposed during S or late S-G2. It is suggested that the normal cells repair the late S-G2 light-induced damage by a caffeine-sensitive repair mechanism that is absent or deficient in the neoplastic cells. It appears that neoplastic cells are deficient in mechanisms for repair of DNA damage induced by light both during pre-S and late S-G2 periods of the cell cycle. (30 Refs)

2. NEWLY SYNTHESISED DNA IN AGEING HUMAN CELLS IN CULTURE TREATED WITH 4-NITROQUINOLINE-1-OXIDE.

Cooke A, Harris WJ
Dept. Medical Genetics, Royal Hosp. for Sick Children, Yorkhill, Glasgow, Scotland
Mech Ageing Dev; 19(2):171-180 1982

Two lines of normal human embryonic lung fibroblasts, MRC-5 and F2002, were serially subcultured until senescence was attained. When cells were exposed to varying concentrations of the chemical carcinogen 4-nitroquinoline-1-oxide (4-NQO), the rate of DNA synthesis (as measured by thymidine incorporation) was reduced in a dose-dependent fashion in cells from both early and late passages. While the overall amount of incorporation was considerably lower in old cells, the extent of inhibition caused by 4-NQO treatment (relative to appropriate controls) was not related to culture age. Alkaline sucrose density gradient analysis of newly synthesised DNA from cells pretreated with 4-NQO failed to detect any significant variation in the size of labeled DNA from cells examined immediately after incubation with radioactive thymidine. The shift of this labeled material to high mol wt in 4-NQO-treated cells also showed no age-related difference. (Author abstract) (26 Refs)

3. IN VITRO ASSAY OF THE EFFECTS OF PSORALENS PLUS ULTRAVIOLET RADIATION ON HUMAN LYMPHOID CELLS.

Kraemer KH
NIH, Building 37, Room 3E24, Bethesda, MD, 20205
JNCI; 69(1):219-227 1982

An in vitro assay system that mimics some of the features of in vivo oral methoxsalen photochemotherapy (PUVA) in relation to human lymphoid cells was developed. In this assay, suspension cultures of human lymphoid cells were subjected to therapeutic concentrations of 8-MOP and to a UVA radiation spectrum modified to approximate the dermal exposure. The assay permitted correlation and quantitation of multiple 8-MOP plus UVA-induced biological and physical alterations in the same assay system. Thus were demonstrated inhibition of DNA synthesis, reduction of cell survival, production of DNA cross-links, and loss of mixed leukocyte reactivity induced by combinations of 8-MOP and UVA in or near the presumed therapeutic range. This assay may be useful for predicting lymphoid cellular toxicity of other photoactive agents as well as for examining the molecular effects of these agents. (Author abstract) (51 Refs)

4. EFFECT OF AGE ON SENSITIVITY OF HUMAN LYMPHOCYTES TO RADIATION. A BRIEF NOTE.

Kutlaca R, Seshadri R, Morley AA
Dept. Hematology, Flinders Univ. South Australia, Bedford Park, South Australia 5042, Australia
Mech Ageing Dev; 19(2):97-101 1982

Survival of human lymphocytes after x-ray and ultraviolet irradiation was studied in individuals of various ages using a technique of cloning in soft agar. There was no effect of age on survival after ultraviolet irradiation but lymphocytes from elderly individuals were approx twice as sensitive to x-radiation as lymphocytes from young individuals. The results are relevant to the possible importance of DNA damage and repair in cellular ageing. (Author abstract) (13 Refs)

BIOLOGICAL ASPECTS OF DNA ALTERATION AND REPAIR IN RELATION TO MUTAGENICITY

5. EFFECT OF COCULTIVATION ON THE LEVELS OF SPONTANEOUS AND INDUCED SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER CELLS.

Rainaldi G, Luccini F, Mariani T
Istito di Mutagenesi e Differenziamento C.N.R., Via Svezia, 10, 56100-Pisa, Italy
J Cell Physiol; 112(2):281-283 1982

Levels of spontaneous and induced sister chromatid exchanges (SCE) were investigated in Chinese hamster cells (line V79/AP4) cultivated in the presence or absence of human cells (C5R0 normal human fibroblasts or xeroderma pigmentosum cell line XP25R0 fibroblasts). V79/AP4 cells were grown exponentially then exposed to UV light or ethylmethane sulfonate (EMS). SCE were determined in homogeneous cell populations (hamster:hamster) and heterogeneous cell populations (hamster:human). Cocultivation of hamster cells with human cells resulted in a reduction of the spontaneous level of SCE and in the level of SCE induced by UV light and EMS. When XP cells were used as a probe instead of normal human fibroblasts, it was shown that XP cells were equally effective in lowering the SCE of Chinese hamster cells damaged either by UV or EMS. The reduction appeared to depend strongly on cell density: culturing the same total amount of cells on larger dishes resulted in a disappearance of the reduction effect. Replacement of human fibroblasts with hamster cells did not affect the influence of cell density on SCE reduction; however, when damaged hamster cells were used, the level of SCE was not lowered. Use of cocultivation is suggested for investigating SCE formation processes. (19 Refs)

6. INTERPRETATIONS ON CHROMIUM MUTAGENICITY AND CARCINOGENICITY (MEETING ABSTRACT).

Petrilli FL, De Flora S
Institute of Hygiene, Genoa, Italy
Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

Thirteen Cr(VI) compounds were positive in the Ames test (TA100 and weakly TA98, TA1538, TA1537), while 1 compound with oxidation state 0 and 7 Cr(III) compounds (unless

contaminated) were negative. Once solubilized, Cr(VI) compounds had a similar mutagenic potency. Cr(VI) also reverted trp- Escherichia coli and preferentially inhibited strains lacking multiple DNA repair mechanisms, ie TM1080 and CM 871. Thus, just below toxic levels, Cr(VI) seems to elicit both frameshift errors and base-pair substitutions, amplified through an inaccurate DNA repair. Various interactions of Cr were also investigated (eg with BaP(benzo(a)pyrene), cigarette smoke condensate, EDTA,ether, crude oil, prostaglandins, oxidizig or reducing chemicals or metabolites). The effects of 32 metabolic systems, including S9 fractions from variously treated animals (rats, mice, trout) or from humans (also under pathological conditions), were investigated. The resulting findings may contribute to interpret carcinogenicity and epidemiologic data. For instance, reduction of Cr(VI) by human gastric juice is consistent with its probable lack of oral carcinogenicity. Also, reversal of Cr(VI) mutagenicity by erythrocyte lysates is consistent with Cr detoxification in the blood and justifies the development of tumors exclusively at implant sites. Conversion of Cr(III) into mutagenic Cr(VI) was afforded only by oxidizing chemicals and not by any of the metabolic systems tested. Conversely, Cr(VI) mutagenicity was decreased by S9 fractions through NADPH-requiring pathways. (no Refs)

7. ANALYSIS BY MICROINJECTION OF THE BIOLOGICAL EFFECTS OF SITE-DIRECTED MUTAGENESIS IN CLONED AVIAN LEUKOSIS VIRAL DNAS.

Pugatsch T, Stacey DW
(c/o Stacey), Roche Inst. Molecular Biology, Nutley, NJ, 07110
J Virol; 43(2):503-510 1982

Cloned avian leukosis viral DNAs were mutagenized in the long terminal repeat, in the leader sequence for env mRNA, and at the pol-env junction. The effect of these mutations in the viral DNA upon its ability to direct virus production or env mRNA synthesis was analyzed by microinjecting the mutant DNAs into chicken embryo fibroblasts and into chicken cells transformed by the env-deficient Bryan strain of Rous sarcoma virus, respectively. The results indicated that: (i) addition of up to 8 base pairs 19 nucleotides upstream of the Hogness box did not block transcription; (ii) deletion of 26 base pairs, including the tRNA primer binding site, allowed synthesis of all viral products and participation in recombination, but replication was blocked; (iii) deletion of fewer than 50 base paris 250 bases downstream of the long terminal repeat depressed expression of all viral genes; and (iv) deletion of most of the gag and pol genes did not inhibit env mRNA synthesis, but virion packaging of the unspliced transcript was inefficient. (Author abstract) (21 Refs)

8. COMPARATIVE CHEMICAL MUTAGENESIS ON THE BASIS OF MOLECULAR DOSIMETRY (MEETING ABSTRACT).

Tates AD
Department of Radiation Genetics and Chemical Mutagenesis, 2333 AL Leiden,, The Netherlands
Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

An essential prerequisite for interspecific comparisons of chemically induced genetic damage in experimental test systems, and extrapolation of these findings to the human situation, is information on the quantitative and qualitative nature of primary and secondary DNA lesions and their persistence. Such knowledge is also indispensable to explore which types of adducts are involved in the genesis of different types of genetic changes. A review will be presented of comparative studies using simple monofunctional alkylating agents (MMS (methyl methanesulfonate), EMS (ethyl methanesulfonate), MNU (methylnitrosourea), DEN (diethylnitrosoamine), ENU, DNN) differing in their reaction pattern with DNA and proteins. Several laboratories are accumulating information on types (eg 3- and 7-alkylpurines, O6-alkylguanine, O2-alkylcytosine, O2-and O4-ethylthymidine, alkylphosphotriesters) and quantities of DNA adducts induced in different cell-types. These findings are correlated with the results of parallel genetic studies. Results obtained by independent investigators indicate that gene mutations induced by EMS and ENU at the HGRPT (hypoxanthine guanine-phosphoribosyl-transferase) locus in Chinese hamster cells correlate with O6-ethylguanine. With respect to the production of SCEs (sister chromatid exchanges) no correlation was found with any of the measured DNA adducts. (no Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN VERTEBRATES

9. DOSE- AND CELL CYCLE-DEPENDENT O(6)-METHYLGUANINE ELIMINATION FROM DNA IN REGENERATING RAT LIVER AFTER [14C]DIMETHYLNITROSAMINE INJECTION.

Rabes HM, Wilhelm R, Kerler R, Rode G
Inst. Pathology, Univ. Munich, Thalkirchner Str. 36, D-8000 Munich 2, W. Germany
Cancer Res; 42(9):3814-3821 1982

To study relations between increased transformation sensitivity during DNA synthesis and carcinogen-induced molecular DNA alterations in regenerating liver, the kinetics of formation and the persistence of alkylated DNA bases were determined 10 to 240 min after a single [14C]dimethylnitrosamine (DMN) injection (1.43 and 4.0 mg/kg) during G1 (12 hr after partial hepatectomy) and in synchronized S phase (4 hr after continuous infusion of hydroxyurea after partial hepatectomy; about 80% hepatocytes in DNA synthesis). At 120 min after administration of DMN, the molar fraction of 7-methylguanine reached a maximum which was proportional to the injected DMN dose in G1 but lower by about 25% in S-phase cells. During G1, the molar fraction of O(6)-methylguanine revealed the same formation kinetics as 7-methylguanine; but in S-phase cells, it was reduced by 60% after 1.43 mg/kg and by 35% after 4.0 mg/kg. 3-Methyladenine reached its maximum earlier in S phase than in G1, with a faster decline in S than in G1. As soon as 10 min after DMN was given, the O6-methylguanine/7-methylguanine ratio was significantly lower in S-phase cells than in G1 cells, with a rapid further decrease during 30 min shortly after carcinogen exposure during DNA synthesis. This rapid repair was less expressed after 4.0 mg/kg, indicating an exhaustion of this process after higher carcinogen doses. Cell cycle-dependent differences of the kinetics of O6-methylguanine and 3-methyladenine in DNA in vivo confirm earlier observations in vitro that these adducts are released by different enzymatic mechanisms the activity of which appears to be enhanced during DNA synthesis in rat liver. The faster elimination of the promutagenic O6-methylguanine during DNA synthesis could represent an important but, because of its saturation at higher carcinogen dosages, not sufficiently effective mechanism to protect proliferating cells from initiation during

the most critical period of the cell cycle. (Author abstract) (56 Refs)

10. IN VITRO REPLICATION OF DNA CONTAINING O6-METHYLGUANINE - KINETIC EVIDENCE OF MUTAGENIC POTENTIAL OF THE ALKYLATED BASE (MEETING ABSTRACT).

Snow ET, Foote RS, Mitra S
University of Tennessee-Oak Ridge Graduate School of Biomedical Sciences, Oak Ridge, TN, 37830
Fed Proc; 41(3):686 1982

O6-alkylguanine (m6G) is believed to be the primary promutagenic lesion produced by simple alkylating carcinogens. In order to study the base-pairing specificity of m6G, we have synthesized poly(dT,m6dG) and poly(dT,dG) with attached oligo (dA) hairpin primers. With T5 phage DNA polymerase, poly(dT, dG) directed incorporation of only dCMP (cytidine monophosphate) and dAMP; however, both dCMP and dTMP (thymidylate), in addition to dAMP, were incorporated with poly(dT,m5dG). The Kmapp of dTTP (thymidine triphosphate) when used singly in the presence of excess dATP with poly(dT,m6dG) are 24 and 200 uM, respectively. The incorporation of dCMP is competitively inhibited by dTTP and the Kiapp for dTTP is equal to its Kmapp. With activated calf thymus DNA, the Kmapp values for all four dNTPs (deoxynucleoside triphosphate) vary from 0.7 to 2.3 uM. Finally, the rate of replication of poly(dT,m6dG) is less than that of poly(dT,dG). This suggests that m6dG, in addition to its preferred base pairing with T, may act as a temporary block during DNA synthesis in vitro. (no Refs)

11. ENZYMATIC REMOVAL OF RING OPENED ALKYLATED GUANINES FROM DNA (MEETING ABSTRACT).

Chetsanga CJ, Batenjany M, Mainwaring M
University of Michigan-Dearborn, Dearborn. MI, 48128
Fed Proc; 41(3):927 1982

We have been studying the effects of a number of carcinogens that bind to either the N-7 or C-8 position of guanine on the subsequent fate of such alkylated guanines in DNA. An interesting finding, also corroborated by other laboratories, has been that the binding of bulkier alkylating agents like phosphoramide mustard (N-7 site), aflatoxin B1 (N-7), and aminofluorene (C-8) to guanine results in imidazole ring fission at the C8-N9 bond in 20% of guanine adducts at neutral pH. With 7-methylguanine or 7-ethylguanine, ring fission to generate formamidopyrimidine only occurs in alkali. The DNA glycosylase that we earlier reported to remove ring opened 7-methylguanines from DNA also removes guanines that spontaneously undergo ring fission at pH 7.2 when alkylated by bulky alkyl groups. The ring fission in 7-methylguanine first converts C-8 to formyl groups some of which are lost until equilibrium is established between formylated and deformylated ring opened guanine adducts. The DNA glycosylase excises the formylated species of ring opened 7-methylguanine. The enzyme also excises the non-formylated ring opened guanines containing bulky alkylating groups at the C-8 position. Our results suggest that such bulky substituent groups may provide an environment conducive to stereospecific recognition of ring opened guanine adducts by the enzyme. (no Refs)

12. COMPARISON OF NUCLEOID AND ALKALINE SUCROSE GRADIENTS IN THE ANALYSIS OF INHIBITORS OF DNA REPAIR IN HUMAN FIBROBLASTS.

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Biochem Biophys Res Commun; 107(1):250-257 1982

Effects of the DNA repair inhibitors hydroxyurea (HU), aphidicolin (APH), cytosine arabinoside (ARAC), dideoxythymidine (dDT), and 3-aminobenzamide (AB) on nucleoid and alkaline sucrose sedimentation patterns of DNA from normal human fibroblasts (2498, BD, ANA-1) or embryonic cells (MRC-5) following UV-irradiation were investigated. Single-strand breaks produced by inhibition of DNA repair by APH maintained complete relaxation of DNA during nucleoid sedimentation, but those produced by ARAC or dDT did not. Skin and embryonic fibroblasts differed in the rate at which their nucleoids recovered rapid sedimentation rates after irradiation, despite similarities in repair. Embryonic cells had a more rapid growth rate and a larger fraction of cells in DNA synthesis than the skin fibroblasts. These differences may have modified the changes in sedimentation rate that are due to excision repair itself. The absence of any effect of AB on nucleoid sedimentation indicated that poly(ADP-ribose) synthesis was not involved in the repair of UV damage in human fibroblasts. Results indicated that the two kinds of gradients employed here cannot be used interchangeably, but can provide useful insights into the intermediate stages of DNA repair in comparative studies. (19 Refs)

13. METHODS FOR THE DETECTION OF SINGLE-STRAND BREAKS IN DNA UNDER NEUTRAL CONDITIONS AND THEIR APPLICATION IN A STUDY ON THE MECHANISM OF REPAIR OF N-METHYLATED PURINES IN MOUSE CELLS.

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Institut fur Molekularbiologie der Universitat Wein, Wasagasse 9, A-1090 Wien, Austria
Eur J Biochem; 125(1):151-156 1982

Considering enzymatic activities found in bacteria and in animal cells, there are two possible mechanisms for repair of N-methylated purines produced by methylating agents such as the mutagen and carcinogen N-methyl-N'-nitro-N-nitrosoguanidine. Both mechanisms involve first an enzymatic removal of the methylated based by glycosylases. The resulting apurinic sites could then be repaired by (a) direct insertion of the correct bases purine insertases or (b) opening of the polynucleotide chain by apurinic endonuclease followed by repair synthesis. As the methods commonly used to detect lesions induced by methylating agents involve alkali, it was thus far not possible to decide between the above possibilities because apurinic sites are by themselves alkali labile. In this paper I describe two methods which avoid alkali and therefore allow the clarification of some aspects of the repair reaction. One of these methods makes use of 95% formamide at 40 C in place of alkali to denature DNA with pre-existing single-strand breaks, the other measures the capacity of DNA scissions with free 3'-OH groups to act as primer for Escherichia coli DNA polymerase I. Results obtained with both methods make it unlikely that purine insertases play a major role in the repair of apurinic sites. Kinetics of production and repair of single-strand breaks, produced in 3T6 mouse fibroblasts by incubation with N-methyl-N'-nitro-N-nitrosoguanidine, were also examined using

the methods of alkaline elution and alkaline sucrose gradient centrifugation. (Author abstract) (29 Refs)

14. INHIBITORS OF POLY-(ADENOSINE DIPHOSPHORIBOSE) SYNTHESIS SLOW THE RESEALING RATE OF X-RAY-INDUCED DNA STRAND BREAKS.

Zwelling LA, Kerrigan D, Pommier Y
Building 37, Room 5D17, 9000 Rockville Pike, Bethesda, MD, 20205
Biochem Biophys Res Commun; 104(3):897-902 1982

In an attempt to elucidate the processes involved in the repair of x-ray-induced single strand breaks (SSB), the resealing rate was quantified in L1210 cells in the absence or presence of inhibitors of poly-(adenosine diphosphoribose) synthesis using the highly sensitive alkaline elution technique. Cellular DNA was radiolabeled with (2-14C)thymidine or (methyl-3H) thymidine. The L1210 cells were irradiated with 300 R or 3,000 R at ice temperature; rate of resealing was measured at 37 C for 15 min. Both inhibitors, 5-methylnicotinamide and 3-aminobenzamide (ABA), slowed, but did not prevent x-ray-induced DNA break resealing. In a separate experiment in which L1210 cells were irradiated with 3,000 R and SSB subsequently quantified following longer incubation periods, over 90% of the SSB were resealed in 60 min even in the presence of 5 milliM ABA. Estimates of time to reach 90% resealing were 23 min without ABA and 55 min with ABA. Preincubating cells in 5 milliM ABA for 1 hr prior to x-radiation had no effect on either the SSB-frequency produced by 3,000 R or on the subsequent resealing rate. The study suggests that x-ray break resealing may proceed in two ways, one associated with poly(-adenosine diphosphoribose) synthesis and one independent of its synthesis. (26 Refs)

15. EFFECT OF HYPERTHERMIA ON THE REPAIR OF RADIATION-INDUCED DNA STRANDBREAKS IN MAMMALIAN CELLS (MEETING ABSTRACT).

Jorritsma JB, Konings AW
Laboratory for Radiopathology, 9713 BZ Groningen, The Netherlands
Int J Radiat Biol; 42(1):72 1982

The effect of hyperthermia on the induction and repair of radiation-induced strandbreaks has been investigated in Ehrlich ascites cells cultured in vitro. For the determination of strandbreaks a modification of the alkaline unwinding method was used. Hyperthermia alone induced strandbreaks only at high hyperthermic doses (eg 2 hours 43C; 45 min 45C). When heat treatments were immediately followed by X-irradiation at 0 C with a dose of 6 Gy, a heat-dose-dependent inhibition of the repair of x-ray-induced strandbreaks could be demonstrated. A heat pretreatment of 2.5 hours 42C resulted in a significantly lower rate of strandbreak repair. Longer heat pretreatment at 42C did not augment this effect. At higher pretreatment temperatures (43, 44 and 45C) inhibition of strandbreak repair took place after shorter pretreatment time periods, and this inhibition increased with increasing heat dose. On the level of initially induced strandbreaks no synergism between hyperthermia and irradiation could be detected. The magnitude of inhibition of strandbreak repair as caused by the different heat pretreatments seems to correlate with the initial survival levels after the hyperthermic treatment alone. (1 Ref)

16. A FLUORESCENCE ENHANCEMENT ASSAY FOR CELLULAR DNA DAMAGE.

Kanter PM, Schwartz HS
Dept. Experimental Therapeutics, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Mol Pharmacol; 22(1):145-151 1982

The bisbenzamide fluorescence enhancement assay for measurement of DNA damage in murine leukemia cells is described. In this assay DNA lesions are expressed by time-dependent alkaline denaturation, which results in unwinding points in the DNA. DNA damage, either by frank strand breakage or by introduction of alkaline labile lesions, yields more unwinding points and single-stranded DNA. The amount of DNA present in duplex and single-stranded form can be measured by enhanced fluorescence of DNA induced by bisbenzamide. Calibration with P388 (mouse ascites) and L1210 (tissue-culture adapted) cells demonstrated that the assay was sufficiently sensitive to detect damage induced by 100 rads x-rays. Comparison of numbers of radiation-induced breaks per relative molecular mass of DNA by enhancement assay and hydroxylapatite chromatography gave nearly identical results using L1210 cells exposed to x-rays. P388 cells were placed in short-term culture and exposed for (2-4 hr) to various concentrations of actinomycin D, 1,3,-bis-(2-chloroethyl)-1-nitrosourea, daunorubicin, Adriamycin, carminomycin, bleomycin, 4'-(9-acridinylamino)-methansulfon-m-aniside, hycanthone, and neocarzinostatin, and dose-response relationships were established for all compounds. Of the antineoplastic agents used, only the anthracyclines appear to interfere with formation of the bisbenzamide-DNA complex. (19 Refs)

17. REEVALUATION OF A DNA BINDING ACTIVITY WITH SPECIFICITY FOR CHEMICALLY MODIFIED DNA.

Chou RH, Tang MS, Cohn SM, Lieberman MW
Div. Hematology, Univ. Pittsburgh Sch. Medicine, Pittsburgh, PA, 15261
Carcinogenesis; 3(6):719-721 1982

A DNA binding activity which appeared in direct filter binding assays to show specificity for DNA modified by N-acetoxy-2-acetylaminofluorene (AAF), N-methyl-N-nitrosourea and methylmethanesulfonate has been further purified and characterized. Equilibrium competition binding experiments indicate this activity shows little, or no, preferential binding of AAF-modified DNA compared to single-stranded DNA and only a small preference compared to uv-irradiated DNA or double-stranded DNA. These findings demonstrate the difficulty of using direct filter binding assays when purifying proteins with a desired biological function and the need to perform competition assays when evaluating specificity. (Author abstract) (10 Refs)

18. OCCUPATIONAL AND IN VITRO EXPOSURE TO STYRENE ASSESSED BY UNSCHEDULED DNA SYNTHESIS IN RESTING HUMAN LYMPHOCYTES.

Pero RW, Bryngelsson T, Hogstedt B, Akesson B
Wallenberg Lab., Biochemical and Genetic Ecotoxicology, Univ. Lund, Box 7031, S-220 07 Lund 7, Sweden
Carcinogenesis; 3(6):681-685 1982

Lymphocytes from 38 individuals occupationally exposed to styrene concentrations in workroom air of 1 ppm to 40 ppm were examined for any genotoxic effects using unscheduled DNA synthesis (UDS) as the indicator of DNA damage. The mean level of N-acetoxy-2-acetylaminofluorene (NA-AAF) in-

duced UDS was significantly increased (p less than 0.001) for the styrene exposed group when compared to the mean level for the unexposed controls. There was no significant effect on uv-induced UDS from the in vivo styrene exposure. Lymphocyte cultures exposed in in vitro to styrene concentrations up to 100 uM have confirmed the UDS data collected on individuals occupationally exposed to styrene. In addition, the in vitro study has also shown that the increased NA-AAF induced UDS resulting from styrene exposure was paralleled by a similar increase in NA-AAF binding to DNA. Taken together these results indicate that styrene exposure does not inhibit DNA repair synthesis, but rather it predisposes lymphocytes to an increased risk for DNA damage induction from subsequent genotoxic exposures. (Author abstract) (31 Refs)

19. REPAIR IN EHRLICH ASCITES TUMOR CELLS.

Wanna-Nakamura SS
University of Illinois at Urbana-Champaign, Urbana, IL
Diss Abstr Int [B]; 42(7):2728-B 1982

Unscheduled DNA synthesis (UDS), an indicator of excision repair, was induced in freshly drawn Ehrlich ascites tumor cells (EAT), using ionizing radiation, far ultraviolet light (254 nm) or near UV light (365 nm) in combination with 8-methoxypsoralen. UDS was scored by grain counts in autoradiographs following the incorporation of tritium-labelled thymidine. The amount of UDS after each of these agents was expressed in terms of two parameters, viz number of cells showing repair and the mean number of grains per nucleus. The influence of radiation dose and of the duration of radioactive thymidine incubation were also examined. To test for a possible relationship between low mitotic index and repair capability, EAT cells were incubated in buffered salt media to lower the mitotic index. Cells kept in a buffered salt solution for 7 hours show a marked drop in mitotic index compared to those incubated in minimal medium containing 15% fetal calf serum (MEM + FCS). This drop in mitotic index was reversible for up to 5 hours, if cells were returned to MEM + FCS. Cells incubated in MEM + FCS also showed a decrease in mitotic activity compared to freshly drawn cells. This reduced mitotic index is approximately constant for up to 24 hours. With the drop in mitotic index, EAT cells also show a drop in repair compared to freshly drawn cells. The repair capability of cells incubated in buffer can be restored by returning cells to MEM + FCS. (no Refs)

20. ENHANCEMENT OF ULTRAVIOLET-INDUCED UNSCHEDULED DNA SYNTHESIS IN HELA CELL LYSATE BY APHIDICOLIN IN VIVO.

Hanaoka F, Yamada K, Kato H, Yamada M
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Biochem Biophys Res Commun; 107(1):1-5 1982

The effect of DNA synthesis inhibitors on UV-induced unscheduled DNA synthesis in HeLa cells and in cell-free homogenates was investigated. Aphidicolin inhibited unscheduled DNA synthesis (UDS) at UV damaged sites in cellular DNA. This inhibition was reversible in cell free homogenates fortified with sufficient deoxynucleotide-triphosphates. A linear and parallel correlation was observed between UDS in intact cells and incorporation of tritiated deoxythymidine triphosphate in homogenates. Combined treatment with aphidicolin and hydroxyurea induced higher UDS in cell-free homogenates than did aphidicolin alone. 2',3'-Dideoxythymidine and arabinofuranoysl cytosine had little effect on UDS. (17 Refs)

21. STUDIES ON INITIATION OF HEPATOCARCINOGENESIS BY N-METHYL-N-NITROSOUREA IN THE RAT.

Cayama EJ
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Diss Abstr Int [B]; 42(10):4024-B 1982

Experiments were designed to: (i) determine whether the enhancement of hepatocarcinogenesis by cell proliferation could be mediated, at least in part, by an increase in initiation, and if that were the case, whether one round of cell proliferation must occur prior to the repair of a carcinogen-induced critical lesion. Initiation was assayed by selectively stimulating the initiated cells to grow into foci of gamma-glutamyl-transpeptidase (GGT)-positive hepatocytes. (ii) determine whether the replication of carcinogen-damaged DNA is important for the participation of cell proliferation in initiation. Hydrocortisone (HC) was given to N-methyl-N-nitrosourea (MMU)-treated animals in mulitple doses in order to inhibit DNA synthesis following PH (partial hepatectomy) (iii) identify the lesions induced in DNA by the carcinogen which permits in vivo replication. (iv) determine the fate of initiated cells. The results obtained indicated that foci of GGT-positive hepatocytes were seen only in rats that received MNU coupled with a cell proliferative stimulus such as PH, but not when such a stimulus was absent. The cell proliferative stimulus had to be given within 24 hours following the carcinogen administration to obtain the maximum number of foci. Similarly, hepatocellular carcinoma was observed 1 year after initiation only when the administration of MNU was coupled with PH. (no Refs)

22. CARCINOGEN BINDING AND DNA REPAIR IN PRIMARY CULTURES OF RAT HEPATOCYTES.

Green CE
University of California, Davis, CA
Diss Abstr Int [B]; 42(9):3649-B 1982

The objectives of these studies were to develop an assay with cultured hepatocytes serving as both the metabolizing component and the target cell for cytotoxicity and genotoxicity and to use this system to study three known or suspected carcinogens-senecionine, aflatoxin B1 (AFB1) and aflatoxin M1 (AFM1). Senecionine, a pyrrolizidine alkaloid from Senecio vulgaris, was a potent cytotoxin, as evidenced by the leakage of lactate dehydrogenase from the hepatocytes into the surrounding culture medium and the loss of cells from the monolayer. Senecionine was also genotoxic, stimulating DNA repair. A nontoxic dose of (14C) senecionine was rapidly absorbed by the hepatocytes and converted to more polar metabolites recovered in the culture medium. AFB1 produced by Aspergillus flavus, and a hydroxylated metabolite, AFM1 were both toxic to cultured hepatocytes at very low doses. However, AFB1 was cytotoxic at lower doses than AFM1. The stimulation of DNA repair was apparent at even lower doses than cytotoxicity. AFB1 was again more potent than AFM1, stimulating DNA repair at 0.025 ug/culture, compared to the low genotoxic dose AFM1 of 0.05 ug/culture. The metabolism of a low dose of (14C)AFB1 and (3H)AFM1 by cultured hepatocytes differed significantly. After one hour, only 50% of the (14C)AFB1 remained unchanged in the cultured medium, while 18 hours were required for the same amount of (3H)AFM1 metabolism to occur. (14C)AFB1 and (3H)AFM1 were metabolized to polar metabolites recovered in the aqueous phase after chloroform extraction and to reactive forms which became covalently bound to cellular macromolecules. (no Refs)

23. NICKEL DISTRIBUTION AND DNA LESIONS INDUCED IN RAT TISSUES BY THE CARCINOGEN NICKEL CARBONATE.

Ciccarelli RB, Wetterhahn KE
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Cancer Res; 42(9):3544-3549 1982

DNA lesions in nuclei isolated from rat tissues following ip injection of the carcinogen nickel carbonate were measured by the alkaline elution technique. Kidney, liver, lung, and thymus gland nuclei were examined at 3 and 20 hr after treatment for the presence of DNA single-strand breaks and cross-links. Single-strand breaks were detectable in lung and kidney nuclei, and both DNA-protein and DNAS interstrand cross-links were detectable in kidney nuclei. No DNA damage was observed in liver or thymus gland nuclei. A dose response to both single-strand breaks and cross-links was observed in kidney nuclei. Time course studies revealed that maximum DNA damage in kidney nuclei occurred at 2 to 4 hr following injection and also revealed the presence of an active repair process in these nuclei. Repair-resistant DNA-protein cross-links were observed to persist through 48 hr. Tissue and intracellular nickel concentrations as measured by electrothermal atomic absorption spectroscopy were observed to correlate with the levels of DNA damage and repair. A dose response to the concentration of nickel in tissues and nuclei was observed. These results are discussed relative to the solubilization, toxicity, and carcinogenicity of nickel compounds. (Author abstract) (45 Refs)

24. DNA DAMAGE AND SELECTIVE TOXICITY OF DOPA AND ASCORBATE: COPPER IN HUMAN MELANOMA CELLS.

Parsons PG, Morrison LE
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Cancer Res; 42(9):3783-3788 1982

Six of eight human melanoma lines showed increased sensitivity to killing by dopa and by ascorbate:copper compared with two fibroblast strains and four other human cell lines of nonmelanoma origin. Catechol, epinephrine, and alpha-methyldopa, but not 5,6-dihydroxyindole, exhibited a similar degree of selectivity. Toxicity was greatly reduced when brief exposure times or high cell densities were used. Depending upon culture conditions, melanoma cells accumulated more [3H]dopa- and [14C]ascorbate-derived isotopic label within the first 5 min than fibroblasts, but after 1 hr this difference was less marked. The catalase activity in melanoma cells was not less than that in fibroblasts. Using two independent methods to determine each type of damage, dopa and ascorbate:copper were found to induce DNA breaks in both cell types but not DNA repair synthesis or DNA interstrand cross-links. More DNA breaks were found in melanoma cells (two lines) than in fibroblasts. Semiconservative DNA synthesis was inhibited immediately, recovered within 6 hr, and in melanoma cells was again inhibited after 24 hr. RNA synthesis was inhibited less than DNA synthesis. Human cell lines with differential sensitivity to alpha-radiation, ultraviolet light, cross-linking agents, or monofunctional alkylating agents exhibited normal survival levels when treated with dopa or ascorbate:copper. (Author abstract) (36 Refs)

25. DOES CAFFEINE BLOCK DNA ELONGATION OR ENHANCE DNA INITIATION IN BENZO[A]PYRENE-DIOL EPOXIDE I DAMAGED CELLS? (MEETING ABSTRACT).

Bowden GT, Rosenthal H, Fetty M
Division of Radiation Oncology, University of Arizona Medical School, Tucson, AZ, 85724
Proc Am Assoc Cancer Res; 23:257 1982

Evidence that caffeine enhances DNA initiation (DNA replication in sub-replic on size nascent strands) in (+/-)-7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy 7,8,9,10-tetrahydrobenzo[a]-pyrene (B[a]P-diol epoxide I) damaged mouse primary epidermal cells was obtained using the pH step alkaline elution assay. DNA elongation as studied by [3H]-thymidine pulse-chase experiments and alkaline sucrose gradients was not inhibited by caffeine alone. However, it appeared that caffeine did inhibit DNA elongation in B[a]P-diol epoxide I treated cells. There was an accumulation of low molecular weight nascent DNA in B[a]P-diol epoxide I damaged cells treated with caffeine. This accumulation of low molecular weight nascent DNA could be due to a block in DNA elongation or an accumulation of new origins of DNA replication. These possibilities were investigated using the pH step alkaline elution assay. Caffeine alone caused a dose dependent increase in DNA initiation without an effect on DNA elongation. B[a]P-diol epoxide I alone inhibited DNA elongation as shown by a relative increase in sub-replicon and replicon size nascent DNA and a decrease in multiple-replicon size nascent DNA. When B[a]P-diol epoxide I (0.66 uM) treated cells were incubated with caffeine, there was a dose dependent increase in replication origins without a significant effect on the proportion of joined replicons (DNA elongation). (no Refs)

26. DNA REPAIR IN A CONGENEIC PAIR OF MICE WITH DIFFERENT LONGEVITIES.

Collier IE, Popp DM, Lee WH, Regan JD
Graduate Sch. Biomedical Sciences, Univ. Tennessee Oak Ridge, Oak Ridge, TN, 37830
Mech Ageing Dev; 19(2):141-146 1982

The rate of ultraviolet light (UV)-induced DNA excision repair was determined in embryonic cells derived from a congeneic pair of short-lived (C57BL/10.F) and long-lived (C57BL/10) mice. Excision repair was measured by both bromodeoxyuridine photolysis and arabinofuranosyl cytosine inhibition. No difference in rate of repair was observed between the two cell lines. (Author abstract) (23 Refs)

DNA ALTERATION AND REPAIR MECHANISMS IN INVERTEBRATES AND LOWER EUKARYOTES

27. BIOLOGICAL EFFECTS OF RADIATION WITH HEAVY IONS.

Kiefer J
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Naturwissenschaften; 69(6):260-265 1982

Experiments with accelerated heavy ions may contribute to the understanding of biological radiation action. After outlining the theoretical background experiments are described which were carried out at the UNILAC-machine (Gesellschaft fur

Schwerionenforschung, Darmstadt, Germany) where ions up to uranium can be accelerated to maximal specific energies of 10 MeV/u. Yeast cells served as biological test systems with the synthesis of ribosomal RNA (r-RNA), colony-forming ability and mutation induction as experimental endpoints. A relationship between action and energy deposition by individual particles can be demonstrated for the inhibition of r-RNA synthesis, in other cases the ion energy plays also an important role indicating that the interaction of delta-electrons from different particles contributes significantly to the biological effect. (Author abstract) (13 Refs) (In GER)

DNA ALTERATION AND REPAIR MECHANISMS IN BACTERIA

28. ROLE OF DEPURINATION IN MUTAGENESIS BY CHEMICAL CARCINOGENS.

Schaaper RM, Glickman BW, Loeb LA
(c/o Loeb) Joseph Gottstein Memorial Cancer Res. Lab., Univ. Washington, Seattle, WA, 98195
Cancer Res; 42(9):3480-3485 1982

The effect of modifying phichi174 viral DNA by the chemical carcinogens beta-propiolactone, N-acetoxyacetylaminofluorene and anti-benzo[a]pyrene diol-epoxide was investigated by transfecting the modified DNA into Escherichia coli spheroplasts. Modification of the DNA in vitro by each of these agents was mutagenic for the phichi174 amber mutants am3 and am86. Mutagenicity depended on the induction of the 'SOS' response and the host spheroplasts. Heating beta-propiolactone-treated DNA at neutral pH caused strong inactivation such that the number of lethal hits was increased four-fold. Sucrose gradient analysis showed the induction of alkali-labile sites in the heated DNA. The 'nicked circle assay' with double-stranded phichi174 DNA showed greater than 70% of these sites to be apurinic sites. Concomitantly with the production of these new sites, a strong increase in the mutation frequency was observed. This mutagenesis also depended upon the induction of the error-prone SOS response in the spheroplasts, as was previously shown to be the case for mutagenesis at putative apurinic sites induced directly by acid-heat treatment. These results suggest that depurination may be of importance to the mechanism of mutagenesis by beta-propiolactone and other carcinogens. (Author abstract) (25 Refs)

MACROMOLECULAR BINDING OF CARCINOGENS

29. IMMUNOLOGICAL QUANTITATION OF O6-ETHYLGUANINE IN ALKYLATED DNA BY RIA AND ELISA (MEETING ABSTRACT).

Wani AA, Gibson-D'Ambrosio R, Clay C, D'Ambrosio SM
Department of Radiology and Pharmacology, Ohio State University, Columbus, OH, 43210
Fed Proc; 41(3):1202 1982

Alkylation at O6 position of guanine in DNA after in vitro or in vivo exposure to alkylating carcinogens is a major promutational product. Antibodies directed against O6-Ethyl-2-deoxyguanosine (O6-EtdGuo) were obtained by immunizing rabbits with a conjugate of O6-EtGuo and key hole limpet hemocyanin. Two immunological methods [radioimmunoassay (RIA) using O6-Et[8-3H]dGuo as tracer antigen and enzyme-linked immunosorbant assay (ELISA) using hapten-BSA conjugate as antigen] were employed to detect the O6-EtdGua at picomole levels, with practically similar results. The specificity of antibodies was demonstrated by the use of nucleoside analogues as inhibitors in RIA and ELISA. The antibodies cross reacted with O6-EtdGuo, O6EtGua and showed least sensitivity to inhibition by deoxyguanosine and guanosine. This assay system for modified nucleic acid components would be very useful in following the production, persistance and repair of these lesions with a variety of cells and tissues treated with a broad spectrum of alkylating carcinogens. Examples will be given for the quantitation of O6-EtdGuo in DNA exposed to ENU (ethylnitrosourea) in vivo and in vitro. (no Refs)

30. THE USE OF MONOCLONAL ANTIBODIES FOR SENSITIVE DETECTION OF ADDUCTS OF POLYCYCLIC ARMOMATIC HYDROCARBONS TO DNA (MEETING ABSTRACT).

Bean RA, Schoen M, Brocades Zaalberg O, Lohman PH
Medical Biological Laboratory TNO, Rijswijk, Netherlands
Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

A major problem in genetic toxicology is the extrapolation of the results from animal studies to man. The only sensible approach to this question is to study the effects of specific DNA lesions with respect to a certain biological endpoint at the molecular level, and thus to determine the relevance of each of these lesions for the mutagenic and carcinogenic process. In recent years, immunochemical methods have been developed for sensitive detection of low levels of DNA damage. Polyclonal and, more recently, also monoclonal antibodies have been raised against a variety of DNA lesions. In our research program, which is aimed at the study of the organ specificity and species specificity of specific DNA damage in animals after exposure to polycyclic aromatic hydrocarbons, we have used acetoxy-acetylaminofluorene (acetoxy-AAF) as a model DNA damaging agent. Polyclonal and monoclonal antibodies have been raised against the adduct dGMP-AAF (deoxy guanosine monophosphate-AAF). These antibodies have been compared in radioimmunoassays and enzyme immunoassays to detect AAF-lesions in DNA treated with various concentrations of acetoxy-AAF in vitro. The results of these experiments show a difference in the level of sensitivity that can be reached with the two types of antibodies. This is probably due to a difference in the apparent affinity constants of the antibodies. (no Refs)

31. NON-RANDOM BINDING OF N-ACETOXY-N-2-ACETYLAMINOFLUORENE TO CHROMATIN SUBUNITS AS VISUALIZED BY IMMUNOELECTRON MICROSCOPY.

Lang MC, De Murcia G, Mazen A, Fuchs RF, Leng M, Daune M
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Chem Biol Interact; 41(1):83-93 1982

The influence of chromatin structure on the accessibility of DNA to the model ultimate carcinogen N-acetoxy-N-2-acetylaminofluorene (N-Aco-AAF) was investigated by means of an immunoelectron microscopic technique developed recently. A homogeneous population of core particles or trinucleosomes from chicken erythrocytes. was submitted to electrophilic

attack by N-Aco-AAF. After DNA isolation, N-2-acetylaminofluorene (AAF) binding sites were mapped upon the DNA fragments using specific antibodies as a probe. Our results indicate a non-random binding of AAF along the DNA. Our data support the results of previous studies showing a preferential binding on the linker region. (Author abstract) (31 Refs)

32. REACTIVITY OF B AND Z-DNA TOWARDS N-ACETOXY-2-ACETYLAMINOFLUORENE.

Spodheim-Maurizot M, Malfoy B, Saint-Ruf G
Centre de Biophysique Moleculaire, C.N.R.S., 1A, Avenue de la Recherche Scientifique, 45045 Orleans Cedex, France
Nucleic Acids Res; 10(14):4423-4430 1982

Poly d(G-C)-poly d(G-C) in B-form, on one hand, and poly d(G-br5C)-poly d(G-br5C) and poly d (G-m5C)-poly d(G-m5C) in Z-form, on another hand, were treated with [3H] N-acetoxy-2-acetylaminofluorine and the kinetics of these reactions were followed by radioactivity. Covalent binding of carcinogen to the polymers was evaluated after separation of the reacted polymers from non-reacted carcinogen by thin-layer chromatography. We found that B-form polymer reacts twice faster than the Z-form polymers. Proportions of main adducts in the three polymers are almost the same. Results are discussed in relation to the calculated electrostatic potential minima and steric accessibility at the reactive site. (Author abstract) (18 Refs)

33. NUCLEASE-RESISTANT OLIGONUCLEOTIDES WITH 'INVERTED' CIRCULAR DICHROISM ISOLATED FROM POLY [D(G-C)]-POLY [D(G-C)] AND M. LYSODEICTICUS DNA AFTER MODIFICATION BY MITOMYCIN C (MEETING ABSTRACT).

Tomasz M, Tucker D, Lipman R
Hunter College, New York, NY, 10021
Fed Proc; 41(3):1200 1982

Binding of mitomycin C (MC), an antitumor agent, is known to cause a change in the circular dichroism (CD) of poly [d(G-C)]:poly [d(G-C)] and, to a lower extent, of DNA. This type of change may indicate a transition of DNA from B to Z-form, induced by MC binding. To investigate this, we digested MC-modified poly [d(G-C)]:poly [d(G-C)] (binding ratio 0.10 mole MC/mole nucleotide-P) and M lysodeicticus DNA (binding ratio 0.15) with a mixture of nucleases under conditions which result in complete degradation of the control polynucleotides to nucleosides. The MC-modified polynucleotides yielded, in addition to nucleosides an oligonucleotide 'core' in 6% yield from the DNA and 23% yield from the poly [d(G-C)]:poly [d(G-C], having the following properties: size 10-20 nucleotide long; binding ratio, approximately 0.25 (saturation binding); UV spectra, combination of MC and nucleotide; CD, the 'inverted' type, as in the Z-form of poly [d(G-C)]:poly [d(G-C)], accounting for most of the CD change seen in the original modified polynucleotides. These cores may be short pieces of Z-DNA. NMR (nuclear magnetic resonance) and other properties are studied for confirmation. (no Refs)

34. IN VIVO PROTECTION BY INDOLE-3-CARBINOL AGAINST CARCINOGEN COVALENT BINDING TO MOUSE HEPATIC MACROMOLECULES (MEETING ABSTRACT).

Stertzer HG
University of Cincinnati Medical Center, Cincinnati, OH, 45267
Fed Proc; 41(3):1559 1982

Indole-3-carbinol (I3C) is a normal constituent of the human diet and is contained in such cruciferous vegetables as cabbage, broccoli, brussels sprouts and cauliflower. When ingested by rodents, this compound has been shown to induce aryl hydrocarbon hydroxylase activity and to confer some protection against polynuclear aromatic hydrocarbon induced neoplasia. We examined the pattern of microsomal enzyme induction in mice gavaged with I3C in corn oil. Hepatic cytochrome P-450, aryl hydrocarbon hydroxylase, and ethoxyresorufin deethylase reached maximum levels in about 5 days. These and other data suggest that the form of cytochrome P-450 induced by I3C is similar to that produced by aryl hydrocarbons. When mice were gavaged with I3C, followed by gavage with 14C-N-nitrosodimethylamine (NDMA) or 14C benzo(a)pyrene (BaP), there resulted a large decrease in the total amount of radioactivity covalently bound to hepatic macromolecules, when compared with corn oil gavaged controls. This decrease in covalent binding was evident in nuclear, mitochondrial, microsomal and supernatant subcellular fractions, as well as in DNA, RNA and protein in each subcellular fraction where they occur. The decrease in binding of NDMA and BaP metabolites occurred within 1 hr after I3C administration, and therefore appeared to have no relationship to the microsomal enzyme induction discussed above. (no Refs)

35. DETECTION OF N2,3-ETHENOGUANINE IN DNA AFTER TREATMENT WITH CHLOROACETALDEHYDE IN VITRO.

Oesch F, Doerjer G
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Carcinogenesis; 3(6):663-665 1982

The reaction of chloroacetaldehyde, a reactive metabolite of the carcinogen vinyl chloride, with DNA produces in addition to the hitherto known adducts, 1,N6-ethenoadenine and 3,N4-ethenocytosine, an ethenoguanine adduct, namely N2,3-ethenoguanine. This adduct is formed in the reaction of chloroacetaldehyde with the free base as well. After DNA hydrolysis followed by isolation of this new adduct by hplc, its mass spectrum and fluorescence spectrum are identical with those published in the literature for the chemically synthesized N2,3-ethenoguanine. The formation of only this guanine derivative out of several theoretically possible reaction products allows the formulation of a reaction scheme. The absence of 7-(2-oxoethyl)-guanine, another recently detected DNA adduct of viny chloride, in chloroacetaldehyde-treated DNA suggests its origin from the other reactive metabolite of vinyl chloride, chloroethylene oxide. The potential of N2,3-ethenoguanine to lead to misincorporation of deoxythymidine monophosphate opposite to guanine and the high fluorescence of this adduct provide it with potentially high biological significance and ease of analytical monitoring. (Author abstract) (14 Refs)

36. CHARACTERIZATION AND PROPERTIES OF THE DNA ADDUCTS FORMED BY THE HEPATOCARCINOGEN N-METHYL-4-AMINOAZOBENZENE IN TARGET AND NON-TARGET ORGANS.

Tullis DL
University of Arkansas for Medical Sciences, Little Rock, AR
Diss Abstr Int [B]; 42(10):4005-B 1982

The carcinogenic aminoazo dyes, typified by N-methyl-4-aminoazobenzene (MAB), are believed to be metabolized to electrophilic N-sulfonyloxy esters which bind covalently to cellular macromolecules, resulting in the induction of hepatic neoplasia. Since the persistence of DNA-carcinogen adducts has been demonstrated to correlate with the susceptibility of specific tissues to tumor formation, the identity and persistence of the DNA adducts formed by MAB in target (liver) and non-target (kidney and spleen) organs has been determined. In order to produce quantities of adducts sufficient for structural determination, the synthetic ultimate carcinogen, N-benzoyloxy-N-methyl-4-aminoazobenzene (N-BzO-MAB) was reacted in vitro with calf thymus DNA. After enzymatic hydrolysis of the DNA, six MAB-DNA adducts were detected by high pressure liquid chromatographic analysis. In vivo adducts corresponding to all six of the in vitro products were detected after one to five weeks of feeding diets containing 0.06% (3H)MAB. Comparison of the adducts isolated from target and non-target tissues revealed a number of differences during the treatment period; however, the only persistent alteration was the increased levels of 3-(deoxyguanosin-N2-yl)-MAB (N2-dG) in hepatic DNA. N2-dG, therefore, is the adduct most likely to be responsible for the induction of hepatic tumors by MAB. (no Refs)

37. METABOLIC ACTIVATION OF AFLATOXIN B1 AND BENZO(A)PYRENE IN EXPLANT CULTURES OF HUMAN TISSUE (MEETING ABSTRACT).

Grafstrom RC, Autrup H, Trump BF, Harris CC
National Cancer Institute, Bethesda, MD, 20205
Fed Proc; 41(3):330 1982

Binding of aflatoxin B1 (AFB) and benzo(a)pyrene (BP) to DNA was compared in non-tumorous human bronchial (HB), esophageal (HE), colonic (HC), and duodenal (HD) tissues obtained at the time of either surgery or autopsy. Tissues were incubated for 24 hr with radiolabelled AFB or BP at 1.5 M in a chemically defined medium. The binding level of the carcinogens to epithelial DNA varied widely among tissues and individuals. Binding levels of AFB (pmol carcinogen bound to 10 mg DNA) were as follows: HB (mean 16, range 0-92, cases 28); HE (11, 0-35, 11); HC (8, 0-44, 27); and HD (23, 0-46, 11). Binding levels of BP were: HB (25, 0-160, 26); HE (27, 0-104, 11); HC (8, 0-44, 24); and HD (21, 0-58, 10). Thus, the order of mean binding values among the tissues was for AFB: HD greater than HB greater than HE greater than HC, and for BP: HE greater than HB greater than HD greater than HC. In tissues where the metabolism of both carcinogens was studied, binding of BP was generally higher than that of AFB. Analysis revealed no correlation between binding levels of the two carcinogens in any of the tissue types. The results indicate quantitative differences in carcinogen activation among tissues and demonstrate the variation in carcinogen metabolism among individuals. (no Refs)

38. DOSE-RESPONSE FOR BENZO(A)PYRENE METABOLITE-DNA ADDUCTS IN LUNG, LIVER, AND FORESTOMACH OF MICE (MEETING ABSTRACT).

Anderson MW, White CM, Adriaenssens PI
National Institute of Environmental Health Science, Research Triangle Park, NC, 27709
Fed Proc; 41(3):1548 1982

The formation of benzo(a)pyrene (BP) metabolite-DNA adducts in lung, liver, and forestomach of female A/HeJ mice was examined as a function of BP dose (po) ranging from 2 to 1350 umol/kg. The major identified adduct in each tissue at each dose was the 7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy-7,8,9,10 tetrahydro-BP (BPDEI)-deoxyguanosine adduct. The 7beta,8alpha-dihydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydro-BP(BPDEII)-deoxy guanosine adduct and a BP-phenol-oxide-DNA adduct were also observed. The dose-response curves for these adducts were sigmoidal in each tissue. The DNA binding expressed as percentage of exposure dose was largest at a BP dose of 0.3 mmol/kg. The dose-response relationships approached linearity at low doses. Thus, the results of these dose-response studies do not reveal the existence of any threshold dose below which binding of BP metabolites to DNA does not occur. Dose-response curves for binding of BP metabolites to protein were also investigated. The ratio of BPDE-DNA adduct levels to protein binding levels was non-linearly related to exposure dose. Thus, binding of BP metabolites to protein cannot be used as a gauge of BP metabolite-DNA binding. These and similar dose-response relationships for polycyclic aromatic hydrocarbons (PAH) metabolite-DNA adducts should be helpful in the low dose extrapolation problem for PAH carcinogenesis. (no Refs)

39. ISOLATION AND QUANTITATION OF DNA-BOUND BENZO(A)PYRENE METABOLITES: COMPARISON OF HYDROXYAPATITE AND PRECIPITATION PROCEDURES.

Adriaenssens PI, Bixler CJ, Anderson MW
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Anal Biochem; 123(1):162-169 1982

The hydroxyapatite and precipitation procedures are two commonly used methods for isolating DNA, and both have been employed in studies on chemical carcinogenesis. A comparison was made of the specific activity (pmol/mg DNA) of benzo(a)pyrene metabolite-DNA adducts in DNA isolated by the two procedures from the lung, liver, and forestomach of A/HeJ mice given oral benzo(a)pyrene. Total DNA-associated radioactivity per milligram DNA was higher with the precipitation procedure than with the hydroxyapatite method. This was partly due to large amounts of early eluting peaks in the high-pressure liquid chromatography analyses of digests of DNA isolated by the precipitation procedure. However, the specific activities obtained for binding of benzo(a)pyrene-7,8-dihydrodiol-9,10-epoxide isomers to DNA isolated by the two methods were in close agreement. The hydroxyapatite procedure resulted in the isolation of purer DNA and required less time and sample handling than the precipitation method. For isolation of DNA from whole tissue for carcinogen-DNA adduct analysis these properties make the hydroxyapatite procedure superior to the precipitation method. Our findings have important implications when comparing the results of DNA-binding studies which employ different DNA isolation procedures. (Author abstract) (23 Refs)

40. COVALENT INTERCALATIVE BINDING OF BENZO(A)PYRENE-9,10-DIOL-7,8-EPOXIDE TO DNA (MEETING ABSTRACT).

MacLeod MC, Selkirk JK
Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN, 37830
Proc Am Assoc Cancer Res; 23:237 1982

In hamster embryo cells treated with benzo(a)pyrene [B(a)P] covalent binding to nuclear DNA and histone proteins is due to 7,8-dihydroxy-9,10-oxy-7,8,9,10-tetrahydro B(a)P (BPDE). In contrast, another diol-epoxide metabolite 9,10-dihydroxy-7,8-oxy-7,8,9,10-tetrahydro B(A)P (reverse BPDE) apparently binds covalently to non-histone proteins but not to DNA. To explain this difference in specificity, we have used the chemically synthesized anti-isomers of BPDE and reverse BPDE to look for in vitro reaction with purified salmon DNA. We have measured the characteristic fluorescence of the pyrene chromophore in samples of DNA treated with BPDE and reverse BPDE and then repurified to remove non-covalently bound hydrolysis products. With DNA concentration held constant at 50 ug/ml, covalently-bound fluorescence increases linearly with diol-epoxide concentration for both diol epoxides. Binding of reverse-BPDE is about twofold lower than binding of BPDE in what is apparently a single, first-order reaction. The structures of the adducts formed by the two diol-epoxides are very different. Absorbance and fluorescence excitation spectra of reverse-BPDE modified DNA show the 8 nm redshift characteristic of intercalation complexes while BPDE-modified DNA does not. In addition, the BPDE- and reverse-BPDE-modified DNAs exhibit differential susceptibility to acid hydrolysis. Concentrations of Mg++ which block physical intercalation aiso inhibit covalent binding of BPDE and reserve-BPDE. Quantitative differences in these in vitro reactions do not account for the differences observed in cell culture. (no Refs)

41. COVALENT BINDING OF PHOTO-OXIDIZED BENZ[A]ANTHRACENE AND RELATED CARCINOGENIC HYDROCARBONS TO PROTEIN.

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Cancer Lett; 16(2):219-225 1982

Formation of unique photo-oxidized products from benz[a]anthracene (BA), 7,12-dimethylbenz[a]anthracene (DMBA), and 3-methylcholanthrene (MC) in the presence of bovine serum albumin (BSA), and their covalent binding to the protein are reported. Fluorescence and excitation spectra of BA photo-products covalently bound to BSA exhibited considerable changes when compared with the parent hydrocarbon BA. At least two distinct photoproducts with overlapping excitation and fluorescence spectra were formed. The excitation spectrum for the 370 nanometer (nm) fluorescence showed the highest peak at 301 nm, whereas for the 390 nm fluorescence the 326 nm peak was the highest. Using the same purification method, BSA with covalently bound DMBA or MC photoproducts was isolated from UV (365 nm)-irradiated DMBA or MC-BSA complexes. Compared to the BA photoproducts, the DMBA photoproduct had less complicated spectra, exhibiting an excitation peak at 320 nm and fluorescence peaks at 377 and 390 nm. In contrast to DMBA, two photoproducts of MC bound to BSA were formed. One photoproduct had fluorescence peaks at 365 and 380 nm with an excitation peak at 320 nm. While the fluorescence characteristics of a phenanthrene-type product from MC were not available, it was expected to have more blue-shifted excitation and fluorescence maxima. The other photoproduct had fluorescence and excitation peaks almost identical with those of MC, suggesting preservation of the original conjugated double bond system. Results suggested that BA, DMBA, and MC can undergo photo-activation and macromolecular binding as in metabolic activation. (19 Refs)

42. PHOTOSENSITIZED DEGRADATION OF DNA BY DAUNOMYCIN.

Gray PJ, Phillips DR, Wedd AG
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Photochem Photobiol; 36(1):49-57 1982

Visible irradiation of DNA-daunomycin solutions resulted in a decrease of viscosity of the DNA and an increase of the rate of denaturation of DNA in formaldehyde. These changes are consistent with the induction of single-strand breaks in the DNA, some of which pair to cause fragmentation of the DNA. The DNA damage increases with drug:nucleotide ratio up to 0.2 and is diminished beyond that range. The damage also increases with ionic strength up to 0.6 M and is diminished above that value. These results suggest that the non-intercalated form of the drug is involved in the photosensitization process. Radicals that are produced accompanying the degradation have been trapped by 5,5-dimethyl-1-pyrroline-1-oxide and identified as hydroxyl radicals from their ESR spectrum. The DNA photosensitized damage is completely inhibited when hydroxyl radicals are removed by the spin-trap, suggesting a direct role for the hydroxyl radicals in the DNA photosensitized degradation process. The implications of the photosensitized DNA damage and the production of hydroxyl radicals in this process are discussed with respect to the medical uses and chemotherapeutic role of daunomycin. (Author abstract) (47 Refs)

43. SITE-DIRECTED PSORALEN CROSSLINKING OF DNA.

Saffran WA, Goldenberg M, Cantor CR
Dept. Human Genetics and Development, Coll. Physicians and Surgeons, Columbia Univ., New York, NY, 10032
Proc Natl Acad Sci USA; 79(15):4594-4598 1982

A technique has been developed for placing site-specific crosslinks into DNA by using a psoralen derivative containing a sulfhydryl group. Plasmid pBR322 was nicked at the unique BamHI restriction site, and mercurated pyrimidines were introduced by nick-translation. Then the psoralen was specifically directed to this site in the dark through a Hg-S linkage prior to irradiation to form a crosslink. The location of interstrand crosslinks was examined by electron microscopy of Ps I-cut molecules and found to be at or near the BamHI site. (Author abstract) (18 Refs)

EFFECT OF CARCINOGENS ON MACROMOLECULAR SYNTHESES

44. ZINC DEFICIENCY, METHYL BENZYL NITROSAMINE CARCINOGENESIS AND DNA SYNTHESIS IN ESOPHAGEAL MUCOSA OF THE RAT (MEETING ABSTRACT).

Schrager T, Newberne PM
Department of Nutrition and Federal Science, M.I.T., Cambridge, MA
Toxicologist; 2(1):105 1982

Zinc deficiency causes hyperplasia and parakeratosis in the esophageal epithelium of many animal species, and increases susceptibility of this tissue to chemical carcinogens. Male Sprague-Dawley rats were given either a control diet (60 ppm) or a diet deficient in Zn (3 ppm). After one month on these diets, some rats received 2.5 mg/kg body weight methyl-benzyl nitrosamine (MBN), twice a week for three weeks. At the end of the dosing period, one group of control ad libitum animals was switched to zinc deficient diet and one group of zinc deficient was switched to control diet. Zinc deficiency throughout the experiment significantly enhanced tumor incidence. Switching diets gave equivocal results. After one month on diets the zinc deficient diet only, led to much greater DNA synthetic activity than the control diet. Following the first dose of MBN, DNA synthetic activity dropped to background levels for both groups but exceeded background at end of dosing. Ten days after the last dose of MBN, DNA synthesis was significantly greater in the control groups. (no Refs)

45. INHIBITION OF DNA REPLICATION AND REPAIR BY ANTHRALIN OR DANTHRON IN CULTURED HUMAN CELLS.

Clark JM, Hanawalt PC
Dept. Biological Sciences, Stanford Univ., Stanford, CA, 94305
J Invest Dermatol; 79(1):18-22 1982

The comparative effects of the tumor promoter anthralin and its analog, danthron, on semiconservative DNA replication and DNA repair synthesis were studied in cultured human cells. Bromodeoxyuridine was used as density label together with 3H-thymidine to distinguish replication from repair synthesis in isopycnic CsCl gradients. Anthralin at 1.1 uM inhibited replication in T98G cells by 50%. In cells treated with 0.4 or 1.3 uM anthralin an additive effect was observed on the inhibition of replication by ultraviolet light (254 nm). In cells irradiated with 20 J/m2, 2.3 uM anthralin was required to inhibit repair synthesis by 50%. Thus there was no selective inhibitory effect of anthralin on repair synthesis. Danthron exhibited no detectable effect on either semiconservative replication or repair synthesis at concentrations below about 5.0 uM. Neither compound stimulated repair synthesis in the absence of ultraviolet irradiation. Thus, anthralin and danthron do not appear to react with DNA to form adducts that are subject to excision repair. Although both compounds appear to intercalate into supercoiled DNA in vitro to a limited extent, the degree of unwinding introduced by the respective drugs does not correlate with their relative effects on DNA synthesis in vivo. Therefore the inhibitory effect of anthralin on DNA replication and repair synthesis in T98G cells does not appear to result from the direct interaction of the drug with DNA. (Author abstract) (20 Refs)

REVIEWS

46. GENETIC AND FAMILY STUDIES (MEETING ABSTRACT).

Miller RW
Clinical Epidemiology Branch, National Cancer Institute, Bethesda, MD, 20205
American Cancer Society National Conference: The Primary Care Physician and Cancer, June 24-26, 1982, Washington, DC American Cancer Society; :A4 1982

It is important not only to know what causes cancer, but also who is most or least susceptible and why. Family clusters of cancer may occur for genetic reasons. The tumors may be of the same type, of dissimilar types or they may be associated with non-genetic diseases. In one family, for example, seven members developed renal cell carcinoma. The study of unaffected members in the line of descent revealed three more cases. Examination of the chromosomes in lymphocytes and skin fibroblasts revealed that the affected members had a translocation from chromosome 3 to chromosome 8. The patients had no signs of other disease, such as congenital malformations. Examination of relatives too young to have developed renal cell carcinoma revealed that several had the 3/8 translocation and were therefore at high risk of renal cell carcinoma. By frequent examination, the tumor can be detected early, and life-saving treatment promptly administered. Purtilo and his associates have described an X-linked susceptibility to diseases of the B lymphocytes, including lymphoproliferative disorders and fatal infectious mononucleosis. In these families multiple male members develop these diseases, which represent an interaction between host susceptibility and a Epstein-Barr virus (EBV). Production of a vaccine against EBV infection could be tested for its effectiveness in such families. Interactions are also known between host susceptibility and physical agents. The inability of patients with xeroderma pigmentosum to heal DNA damage caused by exposure to sunlight is a case in point. In ataxia-telangiectasia, the patients are unable to heal DNA damage due to gamma radiation exposure. The DNA damage is not the same in the two disorders. Protecting patients with XP from sunlight can prevent or at least delay the occurrence of frequently fatal skin cancer. Protecting patients with AT from therapeutic radiation (for the lymphomas to which they are prone), can prevent acute radiation reaction. From such rarities we have learned a great deal about cancer biology. This new information about host susceptibility and carcinogenic mechanisms may lead to new means for prevention or early detection of cancer. (no Refs)

47. THE FORMATION AND REMOVAL OF SISTER CHROMATID EXCHANGES INDUCED BY CYTOSTATIC DRUGS IN VIVO AND IN VITRO (MEETING ABSTRACT).

Sten M, Lambert B, Ringborg U
Department of Clinical Genetics and Radiumhemmet, Karolinska Hospital, S-104 01 Stockholm, Sweden
Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

Cytostatic drugs used in chemotherapy against malignant diseases are often potent genotoxic agents. Personnel in oncology clinics have been shown to have an increased frequency of sister chromatid exchanges (SCE) in peripheral lymphocytes as well as in increased urine mutagenicity in bacterial assays. We have studied the following questions: 1) Which types of cytostatic agents induce SCE in peripheral lymphocytes in vivo? 2) For how long does the SCE-frequency remain elevated in pe-

ripheral lymphocytes in vivo? 3) Are DNA-repair mechanisms effective in removing SCE-inducing lesions caused by cytostatic agents? The results to be presented are based on studies of cancer patients exposed to either one of the drugs melphalan, CCNU (lomustine), adriamycin, DTIC (dacarbazine), and actinomycin D (Act D). Melphalan and CCNU caused a marked increase in SCE, which disappeared within weeks-months after the cessation of therapy. Adriamycin had a moderate SCE-inducing effect, but no such effect was evident with DTIC or actinomycin D. In human lymphocytes in vitro melphalan, CCNU and adriamycin induced SCE, in contrast to Act D and DTIC. Melphalan induced more SCEs during the S-phase than during early G1-phase, while adriamycin caused about the same number of SCE at these different times in the cell-cycle. In unstimulated, resting G0-lymphocytes there was no apparent repair of melphalan-induced DNA-damage leading to SCE. (no Refs)

48. NONMUTAGENIC CARCINOGENS (MEETING ABSTRACT).

von Borstel RC
Basel Institute for Immunology, Grenzacherstrasse 487, 4005 Basel, Switzerland
Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

Nonmutagenic carcinogens fall into four classes: (1) chemicals which are mutagens, but which have characteristics such that many mutagenic assays fail to detect them under 'standard' conditions. Examples in this class are not necessarily related chemically and are represented by chemicals as diverse as diethylstilbestrol, natulan, and ethionine. (2) Physical agents, which are usually called promoters, simply because their action as an initiator is inconceivable. Examples in this class are asbestos and plastic. (3) The chemical promoters, which must be applied after initiators have been administered in order to enhance carcinogenesis. These chemicals do not form adducts with DNA. The 'type specimens' of the chemical promoters are the phorbol esters. Certain kinds of chlorinated hydrocarbons, which can fall into the first or third classes listed above, or conceivably may induce cancer by an entirely different route. Examples in this class are the polychlorinated biphenls and clofibrate. (no Refs)

49. DNA MODIFICATION AND REPAIR IN THE EXPERIMENTAL INDUCTION OF NERVOUS SYSTEM TUMORS BY CHEMICAL CARCINOGENS.

Kleibues P, Patzschke K, Doerjer G
Pathologisches Institut, Albert Str. 19, 78 Freiburg, W. Germany
Ann NY Acad Sci; 381:290-303 1982

Experimental induction of brain tumors in laboratory animals is reviewed, and experiments concerning the possible covalent reaction of DNA of the target tissue as the essential step in malignant transformation are discussed. Monofunctional alkylating agents that have been shown to induce nervous system tumors include alkylnitrosoureas, dialkylaryltriazenes, and hydrazines and related compounds. Monofunctional aliphatic alkylating agents react at all available nucleophilic sites in DNA bases, but the extent of the reaction varies considerably depending primarily on the reaction type of the particular agent. No correlation between alkylation of DNA and neuro-oncogenic agents has been demonstrated although it has been shown in induction of tumors in other systems. Oncogenesis in the nervous system due to aliphatic alkylating agents may result from deficient DNA repair capacity of O6-alkylguanine in the target tissue. Polycyclic aromatic hydrocarbons most effective in induction of tumors in animals are benzo[a]pyrene (BAP), 3-methylcholanthrene, and 7,12-dimethylbenz[a]anthracene (DMBA). Experiments with adduct formation in various target organs of the rat after administration of BAP indicate that the brain may be deficient in the repair of a wider range of carcinogen-DNA adducts, and that the failure of systematically administered BAP to induce nervous system tumors is due to an extremely low extent of initial reaction with cerebral DNA. Similar experiments with DMBA showed that adduct formation was lowest in the brain of female rats, but that concentrations of major reaction product were 2.5 x higher in the fetal brain than in the maternal brain DNA. The route of application affects the chromatographic profile of reaction products, suggesting that bioactivation responsible for DMBA binding may occur both in the fetus itself and in the maternal organs. (39 Refs)

50. GENETIC EFFECTS OF N-METHYL-N'-NITRO-N-NITROSOGUANIDINE AND ITS HOMOLOGS.

Gichner T, Veleminsky J
Inst. Experimental Botany, Czechoslovak Acad. Sciences, Flemingovo 2, 160 00 Praha 6, Czechoslovakia
Mutat Res; 99(2):129-242 1982

The chemistry and metabolism of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and derivatives of MNNG are reviewed. The mode of interaction of MNNG with DNA and proteins are described. Genotoxic effects on microorganisms, plants, and animals are discussed, including effects on human cells in vitro. Data on carcinogenicity and teratogenicity of MNNG and on genotoxicity of MNNG-homologs are presented. (977 Refs)

51. MOLECULAR ASPECTS OF DRUG PHOTOSENSITIVITY WITH SPECIAL EMPHASIS ON PSORALEN PHOTOSENSITIZATION REACTION.

Pathak MA
Dept. Dermatology, Harvard Medical Sch., Massachusetts General Hosp., Boston, MA, 02114
JNCI; 69(1):163-170 1982

Photosensitization reactions involve phototoxic reactions and photoallergic reactions, which are less common. Common drugs and chemicals that photosensitize humans are listed. Phototoxic reactions include the following: (1) direct photosensitization (Type I reactions), in which the reactions of the triplet-state sensitizer are directly attributable to a component other than oxygen (eg, DNA, proteins, and cell membranes), and (2) indirect photosensitization (Type II reactions), in which the triplet state of a sensitizer reacts first with molecular oxygen, producing an 'active oxygen' intermediate that subsequently reacts with the biologic system. The active oxygen intermediates are singlet oxygen (1O2), superoxide radical anions (O2), and hydroxy radicals. Psoralen-induced skin photosensitization appears to involve both Type I and Type II reactions. The formation of monofunctional and bifunctional psoralen-DNA photoadducts (a Type I reaction) is probably responsible for cell damage, cell death, mutation, and even skin carcinogenesis. The erythema response appears to be the result of a Type II reaction. (Author abstract) (42 Refs)

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As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. CURRENT APPROACHES TO THE EXPERIMENTAL INVESTIGATION OF CHEMICALS IN RELATION TO CANCER OF THE BRAIN.
Swenberg JA, Zimmerman HM, Maltoni C, Kurland L, Laerum OD, Kleihues P, Selikoff I, Heidelberger C
Chemical Industry Inst. Toxicology, Research Triangle Park, NC, 27709
Ann NY Acad Sci; 381:43-53 1982

2. PRODUCTION OF BRAIN TUMORS WITH AROMATIC HYDROCARBONS.
Zimmerman HM
Montefiore Hosp. and Medical Center, 111 East 210th St., Bronx, NY, 10467
Ann NY Acad Sci; 381:320-324 1982

3. ORAL CONTRACEPTIVE STEROIDS AND MALIGNANCY.
Grant E
No affiliation given
Clin Oncol; 8(2):97-102 1982

4. METAL CARCINOGENESIS - WHAT IS REAL (MEETING ABSTRACT).
Furst A
Institute of Chemical Biology, University of San Francisco, San Francisco, CA, 94117
Environmental Analytical Chemistry, Airborne Mutagens and Carcinogens, June 16-18, 1982, Provo, Utah. Electric Power Research Institute 44 pp., 1982.

5. GENETIC EFFECTS OF N-METHYL-N'-NITRO-N-NITROSOGUANIDINE AND ITS HOMOLOGS.
Gichner T, Veleminsky J
Inst. Experimental Botany, Czechoslovak Acad. Sciences, Flemingovo 2, 160 00 Praha 6, Czechoslovakia
Mutat Res; 99(2):129-242 1982

RADIATION CARCINOGENESIS

6. PROBLEMS IN ASSESSING THE CANCER RISKS OF LOW-LEVEL IONIZING RADIATION EXPOSURE. VOLUME 1.
Comptroller General of the United States
(c/o Superintendent of Documents), United States General Accounting Office, Document Handling and Information Services Facility, P.O. Box 6015, Gaithersburg, MD, 20760
Problems in Assessing the Cancer Risks of Low-Level Ionizing Radiation Exposure. Volume 1. Washington, D. C., U. S. General Accounting Office, 85 pp., 1981.

7. PROBLEMS IN ASSESSING THE CANCER RISKS OF LOW-LEVEL IONIZING RADIATION EXPOSURE. VOLUME 2.
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8. RISKS OF NUCLEAR ENERGY AND LOW-LEVEL IONIZING RADIATION. REPORT OF AN AMA ADVISORY PANEL TO THE COUNCIL ON SCIENTIFIC AFFAIRS OF THE AMERICAN MEDICAL ASSOCIATION.
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9. ESTIMATION OF RISK OF CANCER INDUCTION IN POPULATIONS EXPOSED TO LOW-LEVEL RADIATION.
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Invest Radiol; 17(4):342-349 1982

10. EVOLUTION OF THE CONCEPTS AND STANDARDS OF RADIATION PROTECTION.
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Inst. Nuclear Energy Academia Sinica, People's Republic of China
Zhonghua Fangsheyixue Yu Fanghu Zazhi; 1(1):2-12 1981
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11. IONIZING RADIATIONS: DNA DAMAGE, MUTAGENICITY AND MORPHOLOGICAL TRANSFORMATION IN MAMMALIAN CELLS. CARCINOGENICITY IN RODENTS AND IN HUMAN.
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Dept. Oncology, Genoa Univ., Genoa, Italy
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13. THE EPIDEMIOLOGY OF CANCER IN CHINA.
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18. ACUTE MYELOID LEUKEMIA FOLLOWING TREATMENT OF HODGKIN'S DISEASE. A REVIEW.
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20. HEALTH EFFECTS OF EXPOSURE TO DIESEL EXHAUST: IMPACTS OF DIESEL-POWERED LIGHT-DUTY VEHICLES.
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Graduate Sch. Public Health, San Diego State Univ., San Diego, CA
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25. DNA REPAIR: A LABORATORY MANUAL OF RESEARCH PROCEDURES. VOLUME 1 PART A.
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27. RETINOIDS AS CHEMOPREVENTIVE AND ANTICANCER AGENTS IN INTACT ANIMALS (REVIEW).
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28. THE CONTRIBUTION OF THE VIRAL THEORY OF TUMOR ORIGIN TO ONCOLOGY.
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33. GENITAL WARTS: RECENT ADVANCES.
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36. MUTAGEN ASSAY WITH ARABIDOPSIS A REPORT OF THE U. S. ENVIRONMENTAL PROTECTION AGENCY GENE-TOX PROGRAM.
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37. METABOLIC AND MODULATING FACTORS IN TOXICITY AND CHEMICAL CARCINOGENESIS (MEETING ABSTRACT).
Fishbein L

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38. PROCEEDINGS OF THE INHALATION TOXICOLOGY AND TECHNOLOGY SYMPOSIUM HELD IN KALAMAZOO, MI, 23-24 OCTOBER, 1980.

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39. CHEMICAL CLASS SEPARATION AND DETAILED IDENTIFICATION OF GENOTOXIC POLYCYCLIC AROMATIC COMPOUNDS IN AIRBORNE PARTICULATES (MEETING ABSTRACT).

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40. SPONTANEOUS NEOPLASTIC PATHOLOGY IN CONTROL RATS - A REVIEW.

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Centro Ricerca Farmaceutica, Via Tito Speri, 14 Pomezia, Roma, Italy
Vet Hum Toxicol; 24(4):243-247 1982

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